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RESPIRATORY CARE

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47TH YEAR—ESTABLISHED 1956

SPECIAL ISSUE

LIQUID NEBULIZATION: EMERGING TECHNOLOGIES PART I

CONFERENCE PROCEEDINGS

- Design Principles of Devices Currently in Use
- Aerosol Delivery Through an Artificial Airway
- Assessing Nebulizer Performance
- Formulations and Nebulizer Performance
- Nebulizer Therapy for Children
- Economic Aspects
- Regulatory Issues

[1]Fink JB, Power J. Am J Respir Crit Care Med 2001;163:A127. [2]Harvey CJ et al. Eur Respir JI 1997;10:905-909. [3]Fink JB et al. Am J Respir Crit Care Med 1999;159:63-68.
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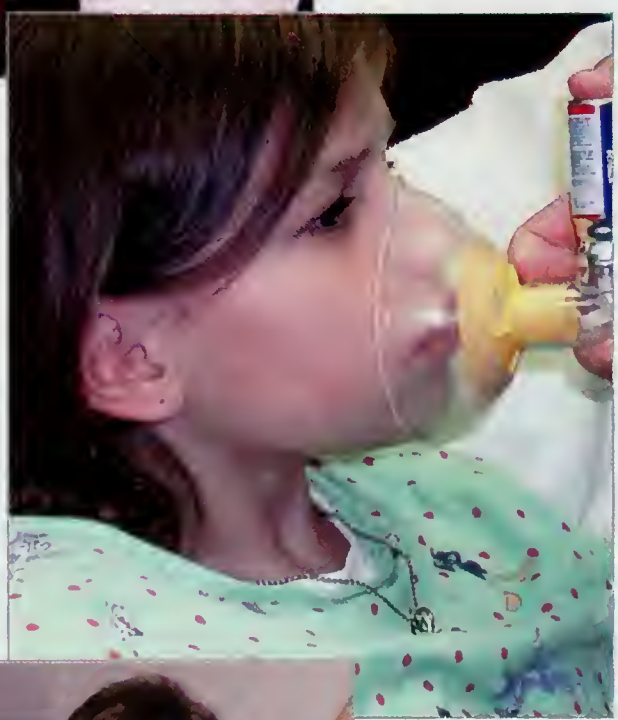

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LIQUID NEBULIZATION: EMERGING TECHNOLOGIES PART I

A SPECIAL ISSUE

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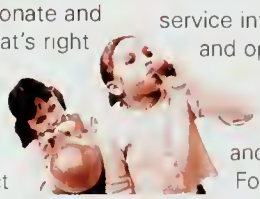

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Editorials, Commentaries, and Reviews to Note

Age-Associated Factors Influencing the Efficacy of Various Forms of Aerosol Therapy—Devadason SG, Le Souef PN. J Aerosol Med 2002;15(3):343-345.

Lung Dose of Inhaled Drugs in Children with Acute Asthma—Le Souef PN, Devadason G. J Aerosol Med 2002;15(3):347-349.

h_2-Agonists: Deja Vu All Over Again: The Second-Generation Controversy (editorial)—Bernstein IL. Chest 2002 Sep;122(3):763-755.

Cephalometric Measurements and Sleep Apnea Hypopnea Syndrome (editorial)—Brown LK. Chest 2002 Sep;122(3):765-768.

Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension—Lepore J, Maroo A, Pereira N, Ginns L, Dec G, Zapol W, et al. Am J Cardiol 2002 Sep 15;90(6):677.

Inhaled Sternids: Too Much of a Good Thing? (editorial)—Wilson JW, Robertson CF. Med J Aust 2002 Sep 16;177(6):288-289.

Diagnosis of Postpneumonectomy Bronchopleural Fistula Using Inhalation of Oxygen or Nitrous Oxide—Mulot A, Sepulveda S, Haberer JP, Alifano M. Anesth Analg 2002 Oct;95(4):1122-1123.

Optimizing Delivery of Inhaled Corticosteroids: Matching Drugs with Devices— O'Riordan TG. J Aerosol Med 2002;15(3):245-250.

Over the past decade, the therapeutic options for delivering inhaled corticosteroids have greatly increased as newer compounds, formulations, and delivery systems have been developed. In the present article, some of the controversies surrounding inhaled steroid delivery systems will be reviewed, concentrating on differences in systemic bioavailability and emphasizing the need to match delivery systems with particular drugs and target populations. The strategies employed to minimize systemic exposure due to absorption of steroid from the gastrointestinal tract include increasing the first pass metabolism of the drug, the use of holding chambers with pressurized metered dose inhalers, and reformulation to create smaller, more respirable, particles. However, because the drugs and devices are not interchangeable, comparisons of the devices based on clinical studies will be confounded by differences in the pharmacology and pharmacokinetics of the drugs. In addition to the interaction of drugs and devices, the needs of different patient populations should influence design of delivery systems. For example, patients without airflow obstruction may have greater sytemic exposure compared to those with obstruction, while young children need different delivery systems from adults. In conclusion, no delivery system can be considered to be intrinsically superior to all others. The delivery system should be judged instead by its ability to optimize the pharmacokinetic properties of the drug, most notably oral bioavailability, and by its suitability for the target subpopulation of asthmatics.

An Investigation of in Vitro/in Vivo Correlations for Salbutamol Nebulized by Eight Systems— Silkstone VL, Dennis JH, Pieron CA, Chrystyn H. J Aerosol Med 2002;15(3):251-259.

The choice of a nebulized system for a patient usually depends on the equipment available. To date, there is limited guidance on the selection and use of a nebulizer. We have conducted in vitro tests described within the draft European Standard for Nebulisers (BSEN13544-1; CEN) and correlated these to in vivo pharmacokinetic performance of relative lung and systemic deposition in healthy volunteers. Eight nebulizer systems have been tested. The in vitro analysis used the recommended CEN methods to quantify the total dose available for inhalation as well as the size distribution from which the respirable dose was determined. The draft European Standard methods were slightly modified to use salbutamol rather than a fluoride tracer. For the in vivo study, nine volunteers provided urine samples after 30 min and then pooled for 24 h after the start of each nebulized dose (2.5 mg of salbutamol). Amounts of salbutamol and its metabolite excreted in the urine samples were determined. There was a significant ($p = 0.02$) correlation between the in vitro respirable dose and the amount of salbutamol excreted in the urine 30 min after the start of nebulization (relative bioavailability of salbutamol to the lung). Also, there was a significant ($p < 0.001$) correlation between the in vitro dose available for inhalation and the total amount of salbutamol and its metabolites excreted over the 24 h after the start of nebulization (relative bioavailability of salbutamol to the body). The results demonstrate that in vivo/in vitro correlations exist and warrant further investigations. The in vitro methods require further validation with in vivo correlations using patients with different severities of airway obstruction.

Inhalation Delivery of Anticancer Agents via HFA-Based Metered Dose Inhaler Using Methotrexate as a Model Drug—Shaik MS, Haynes A, McSween J, Ikediobi O, Kanikkannan N, Singh M. J Aerosol Med 2002;15(3):261-270.

In the present study, the feasibility of delivering anticancer drugs via metered dose inhaler (MDI) was demonstrated using methotrexate (MTX) as a model anticancer drug. MDI formulations of MTX were prepared using hydrofluoroalkane-134a containing 0.67% MTX and 10% ethyl alcohol. The particle size of MTX was reduced by cryo milling with or without a surfactant (Pluronic F77) and the milled drug was employed for MDI formulations, which were subsequently evalu-

ated for their medication delivery, mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Further, the efficacy of aerosolized MTX was evaluated by determining the in-vitro cytotoxicity of MTX against HL-60 cells using a six-stage viable impactor and the induction of apoptosis in HL-60 cells by acridine orange staining. Our results indicate that MTX aerosols having an MMAD varying between 2.2 and 3.2 µm (GSD 2.6-3.7) with a respirable fraction varying between 14.2 and 17.1% could be obtained by using MTX, which was cryo milled either alone or in combination with Pluronic F77. Exposure of HL-60 cells plated in third, fourth, fifth, and sixth stages of viable impactor to two actuations of MDI showed a cell kill of greater than 50%. Further, aerosolized MTX was found to induce apoptosis in HL-60 cells, as assessed by the morphological examination of the cells with fluorescent and confocal microscopy. Our results demonstrate that it is possible to deliver cytotoxic concentrations of MTX in an in vitro system simulating the lower respiratory tract (by using a six-stage viable impactor) via MDI and the cytotoxicity of the aerosolized MTX could be further improved by the optimization of the aerodynamic size.

Improving Drug Delivery from Medical Nebulizers: The Effects of Increased Nebulizer Flow Rates and Reservoirs— Corcoran TE, Dauber JH, Chigier N, Iacono AT. J Aerosol Med 2002;15(3):271-282.

Drug delivery from jet nebulizers can be considered in terms of the dose inhaled and the respirability of that dose. It is proposed that dose respirability and dose per breath can be controlled through specification of the driving gas flowrate, and that the dose inhaled per breath can also be increased through the use of nebulizer reservoirs. When a Hudson Micromist nebulizer was used and assessments of respirability were made utilizing phase Doppler interferometry, it was noted that the portion of the spray mass in droplet sizes of ≤ 5 µm (general respirability) and in droplet sizes of ≤ 3 µm (deep lung respirability) increased linearly with gas

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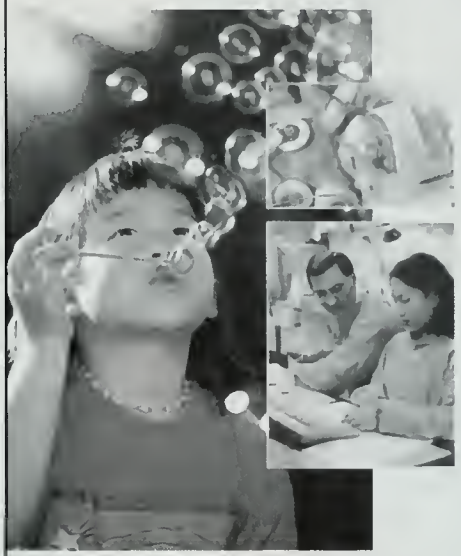

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flowrate for both tank air and helium-oxygen (70/30). Drug mass in the 2-6 μm range (tracheobronchial respirability) peaked at air flowrates of 8-10 L/min and decreased slightly for higher flowrates. Two portable compressors provided respirabilities similar to tank air at the same flowrates. Changing the nebulizer flowrate did not affect the ratio of the inhaled dose to the dose expelled by exhalation when a typical breathing pattern was simulated. A version of the Micromist with an attached reservoir (the Hudson AeroTee) provided a higher dose per breath to the patient and a higher total dose for the same treatment time by conserving the aerosol generated during exhalation. The inhaled dose increased approximately 28% when compared to a standard Micromist, despite significant deposition in the reservoir bag. Nebulizer reservoirs could be used to attain higher doses or to more efficiently utilize expensive medications.

Miniaturized Nebulization Catheters: A New Approach for Delivery of Defined Aerosol Doses to the Rat Lung—Tronde A, Baran G, Eirefelt S, Lennernäs H, Bengtsson UH. J Aerosol Med 2002;15(3):283-296.

A nebulization catheter technique (AeroProbe™) was adapted and evaluated as a new approach for pulmonary delivery of defined aerosol doses to the rat lung. The lung distribution profile was evaluated by dosing Evans blue and Nile blue dye, respectively, to isolated and perfused rat lungs (IPL) and to the lungs of anesthetized and tracheal-intubated rats. The intratracheal aerosol dosing was synchronized with the inspiration of the lungs. Immediately after dosing, the lungs were dissected into upper- and lower trachea, bronchi, and parenchyma. The dye was then extracted from the tissue samples to determine the regional distribution and the recovery of the aerosol dose in the lungs. The droplet-size distribution and the weight of the delivered aerosol dose were analyzed with laser diffraction and gravimetric analysis respectively. The recovery of the delivered dose was high, 99 ± 12 and 105 ± 1%, respectively, in the in vivo administrations and IPL-experiments. The lung distribution profile after aerosol dosing to anesthetized rats was mainly tracheobronchial. Only 12 ± 4% of the dose was recovered in the lung parenchyma. However, after aerosol dosing to the IPL, 38 ± 11% of the dose was distributed to the lung parenchyma. At the settings used, the nebulization catheter aerosolized 1-2 μL of liquid per puff using 1-1.5 mL of air. The droplet-size distribution of the generated aerosols was broad (2-8% <3 μm; 10% <4-7 μm; 50% <10-15 μm; and 90% <20-40 μm). The nebulization catheter technique provides a complement to existing methodology for pulmonary drug delivery in small animals. With this new technique, defined aerosol doses can be delivered into the lungs of rats with no need for aerosol dosimetry.

In Vitro Testing of Two Formoterol Dry Powder Inhalers at Different Flow Rates—Weuthen T, Roeder S, Brand P, Müllinger B, Scheuch G. J Aerosol Med 2002;15(3):297-303.

The efficiency of two different dry powder inhaler systems for the application of the β_2-sympathomimetic drug Formoterol in the lungs has been tested in vitro. Particle size distributions for each device have been measured at four different flow rates (28.3, 40, 60, and 80 L/min) using an Andersen-Impactor. Mass median aerodynamic diameters (MMAD) of the dispersed powder and deposition of the drug in the respiratory tract was determined using a semiempirical lung deposition model. The optimum output for both devices determined by in vitro measurements is supposed to be achieved with flow rates of 40-60 L/min. The Oxis Turbuhaler delivers the smaller particles as the Foradil P Aerolizer and, thus, the Formoterol deeper into the lungs, but the high specific airflow resistance will influence the ability of patients with severe asthma and children to use the system.

Changes in Lung Deposition of Aerosols due to Hygroscopic Growth: A Fast SPECT Study—Chan H-K, Eberl S, Daviskas E, Constable C, Young I. J Aerosol Med 2002;15(3):307-311.

Our objective was to use rapid dynamic SPECT to study the effect of hygroscopic growth on aerosol deposition in the lung. Six healthy volunteers inhaled radiolabeled (^{99m}Tc-DTPA) saline aerosols of two different droplet sizes (MMAD Small 3.2 ± 0.2 and Large 6.5 ± 0.2 μm, span 1.8 and 1.7, respectively) and tonicities (normal saline, NS, 0.9% and hypertonic saline 'HS' 7.0% NaCl) reproducibly on 4 occasions. Simultaneous emission-transmission scanning with a triple detector gamma camera was used to collect the lung images. Regional lung deposition was quantified by the penetration index or PI. The results revealed significant differences of aerosol deposition in the lung, which follows precisely the expectation from particle size and hygroscopicity. The difference in the PI values between the aerosols increases in the order of: Large NS-Large HS < Small NS-Small HS < Small HS-Large NS < Small HS-Large HS < Small NS-Large NS < Small NS-Large HS.

Use of Aerosols for Bronchial Provocation Testing in the Laboratory: Where We Have Been and Where We Are Going— Anderson SD, Brannan JD, Chan H-K. J Aerosol Med 2002;15(3):313-324.

Bronchial provocation testing with pharmacological agents that act directly on airway smooth muscle has important limitations. These include the inability to identify exercise-induced asthma (EIA), to differentiate the airway hyperresponsiveness (AHR) of airway remodelling from the AHR of active inflammation and to differentiate between doses of steroids. Recent studies show that tests that act indirectly to narrow airways are more sensitive than pharmacological agents for identifying airway inflammation and response to treatment. Adenosine monophosphate (AMP) is an indirect challenge that acts on mast cells to cause release of mediators. Hypertonic saline is another and, since its development in the 1980s, has become widely used in Australia. Hypertonic (4.5%) saline is used to identify those with active asthma, those with EIA and those who wish to enter certain occupations or sports (eg, diving). The recent development, again in Australia, of a test that uses dry powder mannitol has promise for use in the laboratory, the office, or for testing in the field. AHR to mannitol identifies people with EIA and is an estimate of its severity. The mannitol response is modified by drugs used to prevent EIA, implying that similar mediators are involved. A mannitol test can be used to monitor response to steroids and is more sensitive than histamine for identifying persistent airway hyperresponsiveness in asthmatics well controlled on steroids. These findings suggest that indirect challenges give more useful clinical information about currently active asthma and the response to treatment than direct challenge and they will become more widely used.

The Role of Particle Properties in Pharmaceutical Powder Inhalation Formulations—Chew NYK, Chan H-K. J Aerosol Med 2002;15(3):325-330.

Pharmaceutical aerosol delivery is undergoing dramatic changes in both inhaler device and formulation aspects. There is a rapid move from the traditional propellant-driven metered dose inhalers to the high performance liquid atomizers and dry powder inhalers (DPIs). DPIs involving the dispersion of powders into aerosols by an inhaler device are particularly attractive as dry powders generally have greater chemical stability than liquids used in atomizers. Delivery of therapeutic proteins as dry powder aerosols is of high commerical interest. However, production and formulation of dry powders for inhalation can be difficult and challenging due to the potential physical instability of the powder. Dry powders consisting of micro- or nano-sized particles are inherently adhesive and cohesive, leading to highly variable dose accuracy and poor aerosol performance. Particle engineering via the use of appropriate pharmaceutical

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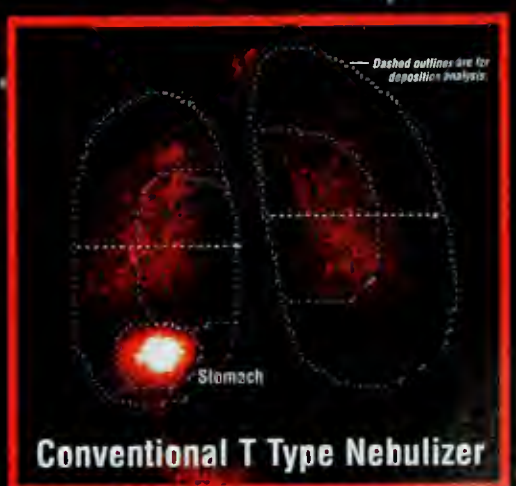

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Photo Source. *Predicting Lung Deposition with a Cascade Impactor*, Sangwan S., Hull F., Condos R., Smaldone GC. *Journal of Aerosol Medicine* 2001; 14(3):421.

excipients and processing parameters can produce particles of optimal morphologies and surface properties which would enhance aerosol generation. Some of the key determinants for successful dispersion of pharmaceutical powders suitable for inhalation are reviewed with an emphasis on the practical significance.

Osmotic Stimuli Increase Clearance of Mucus in Patients with Mucociliary Dysfunction—Daviskas E, Robinson M, Anderson SD, Bye PTP. J Aerosol Med 2002;15(3):331-341.

Mucociliary dysfunction results in mucus accumulation, airway obstruction, bacterial colonization, recurrent infective exacerbations, and an increase in morbidity and mortality. Studies in patients with cystic fibrosis, established that inhalation of hypertonic saline (HS) increases clearance of mucus acutely in a dose-dependent manner. Clearance over 90 min was 23.8 ± 4.0% and 26.0 ± 3.1% in response to 7% and 12% saline, which was significantly enhanced compared to 12.7 ± 1.4% and 19.7 ± 3.1% in response to 0.9% and 3% saline. Mannitol (~300 mg) inhaled as a dry powder had a marked acute effect in patients with bronchiectasis. Clearance over 75 min was 34.0 ± 5.0% with mannitol, 17.4 ± 3.8% with control, and 11.7 ± 4.4% at baseline. Further studies in patients with bronchiectasis showed that mannitol reduces the 24-h retention of radiolabeled mucus, suggesting that the effect of mannitol extends beyond the acute phase. Mannitol helped patients to clear mucus within 2 h that would have taken 24 h to clear without mannitol. A further study in CF patients showed that mannitol was equally effective as 6% HS at improving ciliary and cough clearance. The total clearance over 120 min with mannitol (27.6 ± 3.7%) and with HS (31.0 ± 5.5%) was significantly increased compared to their respective controls (18.6 ± 3.8% and 20.9 ± 3.6%). These preliminary results suggest that long-term treatment with HS or mannitol may benefit patients with mucociliary dysfunction.

Aerosolization of Protein Solutions Using Thermal Inkjet Technology—Goodall S, Chew N, Chan K, Auriac D, Waters MJ. J Aerosol Med 2002;15(3):351-357.

Vapotronics Inc. is developing the thermal inkjet (TIJ) technology used extensively in the printer industry to create a digital aerosol inhaler for the inhalation of therapeutics for local and systemic delivery. The operation of thermal inkjet printers requires generation of high temperatures and vaporization of the liquid formulation to effect droplet ejection. A study was conducted to develop formulations that would permit the generation of aerosols of therapeutic proteins without damage to the inkjet system or degradation of the proteins. Two proteins, human growth hormone and insulin, were formulated and aerosolized. The aerosol was collected and subjected to assays to compare the physicochemical and biological activities of these proteins before and after aerosolization. In each case, there was no significant changes to the proteins as a result of the aerosolization, providing evidence that TIJ can be used for aerosolizing solutions of protein therapeutics.

Aerosols in Bronchiolitis—Barry P. J Aerosol Med 2002 Summer;15(2):109-116.

Bronchiolitis is a common illness of the lower respiratory tract affecting infants that has considerable short and long-term morbidity and occasional mortality. It is the commonest cause of hospitalization for respiratory infection in early childhood, and the seasonal nature of the illness places considerable strain on health care resources during the bronchiolitis season. The youngest infants and those with preexisting cardiorespiratory disease are particularly at risk of severe illness. The treatment of infants with bronchiolitis is largely supportive. There are no therapies that have been proven to reduce the length of the hospitalization or intensive care stay. This paper will review the clinical course of bronchiolitis and discuss the aerosolized therapies that have been proposed for its treatment.

Aerosolized Vasodilators in Pulmonary Hypertension—Gessler T, Schmehl T, Olschewski H, Grimminger F, Seeger W. J Aerosol Med 2002 Summer;15(2):117-122.

Pulmonary hypertension is a life-threatening disease characterized by an increase in artery pressure and vascular resistance in the pulmonary circulation. A primary form of pulmonary hypertension with unknown causes is to be distinguished from the far more frequent secondary forms based on known pulmonary and extrapulmonary disorders. An imbalance in the synthesis of vasoconstrictive and vasodilative agents seems to play an important role in the etiology of pulmonary hypertension. This pathophysiological background offers the possibility to develop treatment strategies, including application of vasodilative drugs. The intravenous administration of vasodilative agents, however, lacks pulmonary selectivity leading to systemic side effects. Therefore, the application of aerosol techniques for alveolar deposition of vasodilatory drugs was proposed and several studies with inhaled iloprost, a stable prostacyclin analogue, demonstrated preferential vasorelaxation in the pulmonary circulation, with the maximum pulmonary vasodilatory potency corresponding to that of intravenous prostacyclin. Clinical experiences with long-term inhaled iloprost are available showing sustained effects on exercise capacity and pulmonary hemodynamics in patients with pulmonary hypertension. Due to the necessary frequent inhalations (up to 12 times a day) and the potency of the prostaglandins, the choice of the nebulizer is critical, requiring physical characterization and device comparison studies under the right heart-catheter conditions. The concept of aerosolized vasodilators is meanwhile well established and offers a promising perspective in the treatment of pulmonary hypertension.

Airway Hyperresponsiveness: Using Bronchial Challenge Tests in Research and Management of Asthma—Sterk PJ. J Aerosol Med 2002 Summer;15(2):123-129.

Bronchal challenge tests have been standardized in detail during the past two decades. They are providing relevant pathophysiological and clinical information about patients with asthma or chronic obstructive pulmonary disease (COPD), by allowing the measurement of the degree of airway hyperresponsiveness, which includes an increased sensitivity as well as increased maximal response to bronchoconstrictor stimuli. There are various types of challenges, to which the responses are not interchangeable. Responses to so-called "indirect" challenges are largely dependent on the state of activation of inflammatory or resident cells within the airways, and the state of activation can vary rapidly, either spontaneously or through intervention. Responses to "direct" challenges are dependent on less variable, rather chronic features of airways inflammation or remodeling. Bronchoprovocation tests provide integrated information about multiple pathophysiological pathways within the airway. This is in contrast to the measurements of cells, mediators, or cytokines in biological fluids, which provide only very specific information on selected inflammatory pathways. It has recently been shown that the outcome of asthma can substantially be improved when long-term treatment is not only guided by symptoms and lung function, but also by the degree of airway hyperresponsiveness to direct stimuli. Taken together, current data warrant a broader usage of bronchoprovocation tests in the research as well as clinical management of asthma and COPD. In asthma, it allows selective, individually targeted therapy of the patient as opposed to the currently recommended regimens that are (increasingly) unselective in their approach. The potential benefits of monitoring other phenotypic disease markers is currently under investigation.

Drug Absorption by the Respiratory Mucosa: Cell Culture Models and Particulate Drug Carriers—Ehrhardt C, Fiegel J, Fuchs S, Abu-Dahab R, Schaefer UF, Hanes J, Lehr CM. J Aerosol Med 2002 Summer;15(2):131-139.

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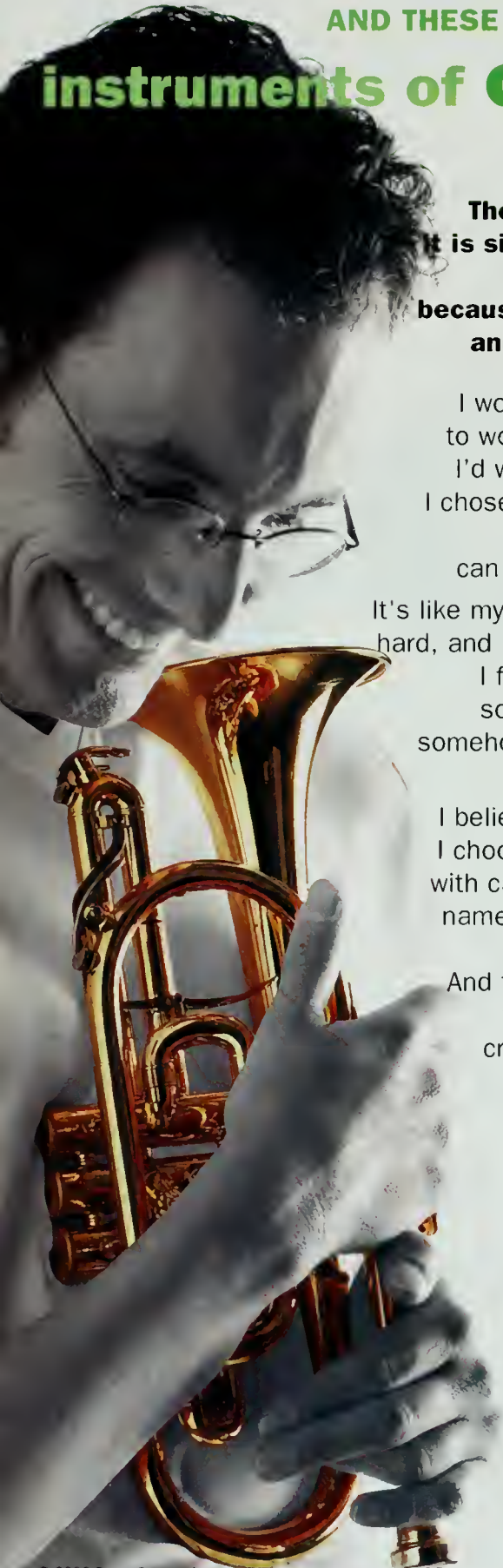

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The inhalation route is of increasing interest for both local and systemic drug delivery, including macromolecular biopharmaceuticals, such as peptides, proteins, and gene therapeutics. In addition to appropriate aerosolization for deposition in relevant areas of the respiratory tract, therapeutic molecules may require an advanced carrier system for safe and efficient delivery to their target. Two approaches to obtain novel carrier systems for pulmonary drug delivery are large porous microparticles with a low aerodynamic diameter and lectin-functionalized liposomes. Epithelial cells of alveolar or bronchial origin, obtained either from patient material or from established cell lines, can be grown on permeable filter supports, resulting in polarized monolayers with functional intercellular junctions. With such in vitro models, transport of drugs into pulmonary epithelial cells and/or across the air-blood barrier, as well as the effect and efficacy of novel drug carrier systems can be systematically studied.

Targeting Delivery of Aerosols to Different Lung Regions—Bennett WD, Brown JS, Zeman KL, Hu SC, Scheuch G, Sommerer K. J Aerosol Med 2002 Summer;15(2):179-188.

With the increasing use of aerosolized drugs, there is a need to understand the means by which these drugs can most effectively be targeted to desired regions of the lung. Several attempts have been made at targeting aerosols in the lung by changing particle sizes and breathing patterns with varying degrees of success. Recent use of such techniques as shallow, aerosol bolus delivery and extremely slow inhalations of aerosols in diagnostic lung tests may also prove beneficial for targeting drug delivery to the conducting airways. This review discusses the potential for utilizing aerosol delivery techniques for selectively targeting aerosol deposition along both serial and parallel pathways in the lung. Based on a review of previous studies concerning factors that determine aerosol and gas distribution in the lung, the potential for utilizing various breathing techniques in concert with variations in particle sizes are considered. Further research on the factors that determine distribution of aerosol in the diseased lung may help in designing successful targeting strategies for the future.

The Pulmonary Toxicology of Ultrafine Particles—Donaldson K, Brown D, Clouter A, Duffin R, MacNee W, Renwick L, Tran L, Stone V. J Aerosol Med 2002 Summer;15(2):213-220.

Ultrafine particles are a component of air pollution, derived from primary combustion sources, and so we have undertaken a programme of study on the mechanisms of lung injury caused by ultrafine particles. Ultrafine particles made of low-solubility, low-toxicity materials are more inflammogenic in the rat lung than fine respirable, particles made from the same material. Ultrafine particles can cause inflammation via processes independent of the release of transition metals, as shown by the fact that soluble products from ultrafine carbon black have no ability to cause inflammation. The property that drives the greater inflammogenicity of ultrafines is unknown but very likely relates to particle surface area and involves oxidative stress. Increases in intracellular Ca(++) may underlie the cellular effects of ultrafines, although the mechanism whereby ultrafines have this effect is not understood. However, increased influx of Ca(++) into macrophages occurs via the membrane Ca(++) channels following contact with ultrafine particles, and involves oxidative stress. Increased Ca(++) in macrophages exposed to ultrafines can lead to the transcription of key pro-inflammatory genes such as TNFalpha. Ultrafine particles can also impair the ability of macrophages to phagocytose and clear other particles, and this may be pro-inflammogenic.

Gene Therapy for Cystic Fibrosis by Means of Aerosol—Rochat T, Morris MA. J Aerosol Med 2002 Summer;15(2):229-235.

Gene therapy by aerosol is an attractive approach for the treatment of cystic fibrosis (CF). Clinical trials with aerosols in CF patients have been conducted by five different groups, three using adenoviral vectors and two using cationic liposomes carrying the coding sequence for the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR). These trials revealed that gene transfer from the lumen to the respiratory epithelium can currently be achieved in vivo, but only with low efficiency and for limited duration. Some of the many hurdles on the way to successful gene therapy for this disease will be discussed in this review. Innovative strategies need to be developed to reach this tantalizing goal.

Evaluation of Young Children in Contact with Adult Multidrug-Resistant Pulmonary Tuberculosis: A 30-Month Follow-Up—Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Pediatrics 2002 May;109(5):765-771.

SETTING: The Western Cape Province of South Africa, an area with a high tuberculosis (TB) incidence, where initial multidrug resistance (MDR) among adult TB cases was 1.1% during 1992-1993. OBJECTIVE: To determine the long-term prevalence of TB infection and disease in children in household contact with adults with MDR pulmonary TB, and to establish the efficacy of chemoprophylaxis in preventing disease in these children. METHOD: Children <5 years old in contact with 73 MDR TB adults were evaluated. Disease was treated by prescribing at least 2 drugs to which the adult's strain was susceptible. The remaining children were classified as infected or noninfected and received chemoprophylaxis according to the index's strain susceptibility or were followed up and treated when indicated. All were followed up for 30 months. RESULTS: At the initial evaluation 125 children were seen, median age 27.5 months. Of these, 119 were followed up. Fourteen (12%) had disease, 61 (51%) were infected only, and 44 (37%) were noninfected. By 30-month follow-up, 29 (24%) had developed disease and 64 (54%) were infected only. Four adult-child pair *Mycobacterium tuberculosis* isolates were compared by DNA fingerprinting; 3 were identical. All children who developed TB disease were clinically cured. Two (5%) of 41 children who received appropriate chemoprophylaxis and 13 (20%) of 64 who did not, developed TB during follow-up (odds ratio: 4.97). CONCLUSION: The study confirms MDR TB transmission to childhood contacts. Seventy-eight percent of children were infected or developed disease. Appropriate chemoprophylaxis may prevent disease in these children.

Efficacy and Safety of Tolazoline for Treatment of Severe Hypoxemia in Extremely Preterm Infants—Nuntnarumit P, Korones SB, Yang W, Bada HS. Pediatrics 2002 May;109(5):852-856.

OBJECTIVE: To determine the efficacy of tolazoline as a rescue treatment for hypoxemia in preterm infants with respiratory distress syndrome. METHODS: Retrospective chart review on case series of infants weighing < 750 g at birth who received tolazoline during a severe hypoxemic episode while receiving maximal ventilator support for respiratory distress syndrome. A slow bolus infusion of low dose tolazoline (0.5 mg-2 mg/kg) mixed with plasmanate or normal saline (10 mL/kg) was administered. Outcome measures evaluated included an increase in P_{aO_2} ≥20 mm Hg from pretreatment value and an increase in oxygen saturation to ≥90%. RESULTS: Forty-three infants with a mean gestational age and birth weight of 24 weeks and 581 g, respectively, received tolazoline. All infants were mechanically ventilated and required a fraction of inspired oxygen of 1.0. Oxygenation improved in 72% (31/43) of infants with a tolazoline dose of 0.5 to 1.0 mg/kg. Of those who responded, P_{aO_2} values (mean ± standard deviation) pretolazoline and posttolazoline were 32 ± 7.5 mm Hg and 156 ± 114.9 mm Hg, respectively. In all responders, oxygen saturation increased to ≥ 90% within 30 minutes of tolazoline administration. Improvement in pH, P_{CO_2}, oxygenation index, and mean airway pressure was also noted. Among nonresponders, pH decreased and P_{CO_2} increased after tolazoline. Minimal change in blood pressure was noted in both responders and nonresponders. Heart rate decreased by 19

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beats per minute among nonresponders compared with an increase of 3 beats per minute in those who responded to tolazoline. CONCLUSION: Tolazoline is an effective treatment of severe resistant hypoxemia in preterm infants who are already on vigorous ventilatory support.

Racial/Ethnic Variation In Asthma Status And Management Practices Among Children In Managed Medicaid—Lieu TA, Lozano P, Finkelstein JA, Chi FW, Jensvold NG, Capra AM, et al. Pediatrics 2002 May;109(5):857-865.

OBJECTIVE: Racial/ethnic disparities in hospitalization rates among children with asthma have been documented but are not well-understood. Medicaid programs, which serve many minority children, have markedly increased their use of managed care in recent years. It is unknown whether racial/ethnic disparities in health care use or other processes of care exist in managed Medicaid populations. This study of Medicaid-insured children with asthma in 5 managed care organizations aimed to 1) compare parent-reported health status and asthma care processes among black, Latino, and white children and 2) test the hypothesis that racial/ethnic variations in processes of asthma care exist after adjusting for socioeconomic status and asthma status. METHODS: This cross-sectional study collected data via telephone interviews with parents and computerized records for Medicaid-insured children with asthma in 5 managed care organizations in California, Washington, and Massachusetts. The American Academy of Pediatrics (AAP) Children's Health Survey for Asthma was used to measure parent-reported asthma status. We used multivariate models to evaluate associations between race/ethnicity and asthma status while controlling for other sociodemographic variables. We evaluated racial/ethnic variations in selected processes of asthma care while controlling for other demographic variables and asthma status. RESULTS: The response rate was 63%. Of the 1658 children in the respondent group, 38% were black, 19% were Latino, and 31% were white. Black children had worse asthma status than white children on the basis of the AAP asthma physical and emotional health scores, symptom-days, and school days missed in the past 2 weeks. Latino children had equivalent AAP scores but missed more school days than white children. On the basis of the AAP asthma physical health score, the black-white disparity persisted after adjusting for other sociodemographic variables. After adjusting for sociodemographic variables and asthma status, black and Latino children were less likely to be using inhaled antiinflammatory medication than white children (relative risk for blacks: 0.69; relative risk for Latinos: 0.58). They were more likely to have home nebulizers. Other processes of asthma care, including ratings of providers and asthma care, use of written management plans, use of preventive visits and specialists, and having no pets or smokers at home, were equal or better for minority children compared with white children. CONCLUSIONS: Black and Latino children had worse asthma status and less use of preventive asthma medications than white children within the same managed Medicaid populations. Most other processes of asthma care seemed to be equal or better for minorities in the populations that we studied. Increasing the use of preventive medications is a natural focus for reducing racial disparities in asthma.

Nebulized Budesonide Inhalation Suspension Compared with Cromolyn Sodium Nebulizer Solution for Asthma in Young Children: Results of a Randomized Outcomes Trial—Leflein JG, Szefler SJ, Murphy KR, Fitzpatrick S, Cruz-Rivera M, Miller CJ, Smith JA. Pediatrics 2002 May;109(5):866-872.

OBJECTIVE: The availability of antiinflammatory asthma medications for infants and young children has been limited. The objective of this study was to compare effects of nebulized budesonide inhalation suspension and cromolyn sodium nebulizer solution on asthma-related health outcomes in young children with asthma. METHODS: We conducted a randomized, parallel-group, 52-week, open-label study in 36 US clinical sites. Patients included 335 children who were 2 to 6 years of age and had persistent asthma that had been treated with at least 1 long-term control medication; 287 children (86%) completed the study. Patients received budesonide inhalation suspension, 0.5 mg daily (n = 168), or cromolyn sodium nebulizer solution, 20 mg 4 times daily (n = 167), for 8 weeks, followed by dose titration at the investigator's discretion. The main outcome measure was the rate of asthma exacerbations over 52 weeks. Secondary measures included times to first asthma exacerbation and first use of additional asthma therapy, asthma symptom scores, rescue medication use, and health care resource use. RESULTS: The budesonide group had a mean (median) asthma exacerbation rate of 1.23 (0.99) per year compared with 2.41 (1.85) for the cromolyn group, significantly longer times to first exacerbation and first use of additional long-term asthma medication, greater improvements in asthma symptom scores, reduced use of rescue medication, and fewer urgent care visits. Both treatments were well tolerated. CONCLUSIONS: Budesonide inhalation suspension was more effective than nebulized cromolyn sodium in young children with persistent asthma. Both treatments were well tolerated with similar adverse event profiles.

Serial Assessment of Mortality in the Neonatal Intensive Care Unit by Algorithm and Intuition: Certainty, Uncertainty, and Informed Consent—Meadow W, Frain L, Ren Y, Lee G, Soneji S, Lantos J. Pediatrics 2002 May;109(5):878-886.

OBJECTIVES: Does predictive power for outcomes of neonatal intensive care unit (NICU) patients get better with time? Or does it get worse? We determined the predictive power of Score for Neonatal Acute Physiology (SNAP) scores and clinical intuitions as a function of day of life (DOL) for newborn infants admitted to our NICU. METHODS: We identified 369 infants admitted to our NICU during 1996-1997 who required mechanical ventilation. We calculated SNAP scores on DOL 1, 3, 4, 5, 7, 10, 14, 21, 28, and weekly thereafter until either death or extubation. We also asked nurses, residents, fellows, and attendings on each day of mechanical ventilation: "Do you think this child is going to live to go home to their family, or die before hospital discharge?" RESULTS: Two thousand twenty-eight SNAP scores were calculated for 285 infants. On DOL 1, SNAP for nonsurvivors (24 ± 8.7 [standard deviation]) was significantly higher than SNAP for survivors (13 ± 6.1). However, this difference diminished steadily and by DOL 10 was no longer statistically significant (12.7 ± 4.9 vs 10.0 ± 4.8). On each NICU day, at all ranges of SNAP scores, there were at least as many infants who would ultimately survive as would die. Consequently, the positive predictive value of any SNAP value for subsequent mortality was < 0.5 on all NICU days. Prediction profiles were obtained for 230 ventilated infants reflecting over 11 000 intuitions obtained on 2867 patient days. One hundred fifty-seven (81%) of 192 survivor profiles displayed consistent accurate prediction profiles-at least 90% of their NICU ventilation days were characterized by 100% prediction of survival. Twenty-five (13%) of 192 surviving infants survived somewhat unexpectedly; that is, after at least 1 day characterized by at least 1 estimate of "death." Thirty-three (60%) of the 55 nonsurvivors died before DOL 10. Eighty-two percent of the prediction profiles for these early dying infants were homogeneous, dismal, and accurate. Twenty-two (40%) of the 55 nonsurvivors died after DOL 10. Seventeen (78%) of these 22 late-dying infants were predicted to live by many observers on many hospital days. Sixty-one (30%) of 230 profiled patients had at least 1 NICU day characterized by at least 1 prediction of death; 26/61 (43%) of these patients were incorrectly predicted; that is, they survived. Seventeen infants who were predicted to die during but survived nonetheless were assessed neurologically at 1 year. Fourteen (82%) of these 17 were not neurologically normal-8 were clearly abnormal, 1 suspicious, and 5 had died. CONCLUSIONS: If absolute certainty about mortality is the only criterion that can justify a decision to withhold or withdraw life-sustaining treatment in the NICU, these data would make such decisions difficult on the first day of life, and increasingly

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problematic thereafter. However, if we acknowledge that medicine is inevitably an inexact science and that clinical predictions can never be perfect, we can ask the more interesting question of whether good but less-than-perfect predictions of imprecise but ethically relevant clinical outcomes can still be useful. We think that they can-and that they must.

Improving Childhood Asthma Outcomes in the United States: A Blueprint For Policy Action—Lara M, Rosenbaum S, Rachelefsky G, Nicholas W, Morton SC, Emont S, et al. Pediatrics 2002 May;109(5):919-930.

BACKGROUND/OBJECTIVE: Asthma is increasingly being recognized as an important public health concern for children in the United States. Effective management of childhood asthma may require not only improving guideline-based therapeutic interventions, but also addressing social and physical environmental risk factors. The objective of this project was to create a blueprint for improvement of national policy in this area. DESIGN/METHODS: A nominal group process with nationally recognized experts and leaders (referred to as "the committee") in childhood asthma. RESULTS: The committee identified 11 policy recommendations (numbered in order below) in 2 broad categories: Improving Health Care Delivery and Financing, and Strengthening the Public Health Infrastructure. Recommendations regarding Improving Health Care Delivery and Financing include the development and implementation of quality-of-care standards in 1) primary care, 2) self-management education, and 3) case-management interventions, and the expansion of insurance coverage and benefit design by 4) extending continuous health insurance coverage for all children, 5) developing model insurance benefits packages for essential childhood asthma services, and 6) educating health care purchasers in how to use them. Recommendations for Strengthening the Public Health Infrastructure include public funding of asthma services that fall outside the insurance system through establishing 7) public health grants to foster asthma-friendly communities and 8) school-based asthma initiatives. 9) Launching a national asthma public education campaign, 10) developing a national asthma surveillance system, and 11) establishing a national agenda for asthma prevention research, with an emphasis on epidemiologic and behavioral sciences, are also recommended. CONCLUSIONS: Implementing these recommendations will require coordination of activities at the national, state, and local community level, and within and outside the health care delivery system. With a further commitment of national and local resources, implementation of these recommendations will likely lead to improved child and family asthma outcomes in the United States. childhood asthma, health care policy, health care services.

Chronic Lung Disease After Activated Charcoal Aspiration –Graff GR, Stark J, Berkenbosch JW, Holcomb GW 3rd, Garola RE. Pediatrics 2002 May;109(5):959-961.

The ingestion of toxic substances is a common pediatric emergency. Activated charcoal is part of the standard treatment for most toxic ingestions and is considered a benign therapy. We report a case of inadvertent administration of activated charcoal into the trachea that resulted in the development of chronic lung disease.

Efficacy and Safety of Low-Dose Fluticasone Propionate Compared with Montelukast for Maintenance Treatment of Persistent Asthma—Meltzer EO, Lockey RF, Friedman BF, Kalberg C, Goode-Sellers S, Srebro S, et al. Mayo Clin Proc 2002 May;77(5):437-445.

OBJECTIVE: To compare the long-term effects of an inhaled corticosteroid with those of a leukotriene modifier on measures of clinical efficacy, subject preference, and safety in patients with persistent asthma. PATIENTS AND METHODS: Between November 17, 1998, and May 26, 2000, we conducted a multicenter, randomized, double-blind, double-dummy, parallel-group study of patients aged 15 years or older with persistent asthma. The patients were symptomatic while taking short-acting β_2-agonists alone and were treated with fluticasone propionate (88 µg [2 puffs of 44 µg] twice daily) or montelukast (10 mg/d) for 24 weeks. Measures of pulmonary function, asthma symptoms, albuterol use, nighttime awakenings, physician assessments of efficacy, patient satisfaction, asthma-related quality of life, and safety were evaluated. RESULTS: A total of 522 patients were randomized to receive fluticasone or montelukast, and 395 patients completed the study. At end point, treatment with fluticasone significantly improved pulmonary function, asthma symptom scores, the percentage of symptom-free days, rescue albuterol use, and the number of nighttime awakenings due to asthma when compared with montelukast ($p \leq 0.002$, each comparison). Significantly more patients were satisfied with fluticasone therapy (83%) compared with montelukast therapy (66%) ($p<0.001$), and fluticasone therapy was rated as effective by a significantly greater portion of physicians (67%) than was montelukast therapy (54%) ($p<0.001$). Treatment with fluticasone significantly improved asthma-related quality-of-life measures compared with montelukast ($p \leq 0.01$). The incidence of asthma exacerbations was similar in the fluticasone (19 patients, 7%) and montelukast (21 patients, 8%) treatment groups, although slightly more patients in the montelukast group were withdrawn from the study because of asthma exacerbations (6% vs 4%, respectively). CONCLUSION: Long-term treatment with a low dose of inhaled fluticasone is more effective than oral montelukast as first-line maintenance therapy for the treatment of persistent asthma.

Patient, Clinician, and Population Perspectives on Determining the Clinical Significance of Quality-of-Life Scores—Frost MH, Bonomi AE, Ferrans CE, Wong GY, Hays RD; Clinical Significance Consensus Meeting Group. Mayo Clin Proc 2002 May;77(5):488-494.

Despite the success of screening and treatment of major cancers in the United States, cancer remains a chronic condition dominated by symptoms and treatment-related adverse effects. Because of these often taxing symptoms and adverse effects, numerous studies have been conducted to document the effects of cancer diagnosis and treatment on the quality of life (QOL) of patients. But there has been limited investigation of the clinical significance of QOL scores. This article examines the clinical significance of QOL scores from 3 key perspectives: patients, clinicians, and the general population. The patient's perspective includes an evaluation of the size of difference in scores that individual patients can detect and regard as important. The clinician perspective relies on whether the clinician believes the patient's condition has stayed the same vs whether changes have occurred (decline or improvement). The population perspective represents a democratic process in which the input or votes of a community of people are used to determine if health state A is clinically significantly different from health state B. While many clinicians and researchers advocate for QOL to be defined from the patient's perspective, the reality is that QOL is often defined by clinicians in terms of observable events. Even when measures are used in which the patient identifies how his or her life has been affected, it is often the clinician who interprets the clinical importance of this information. The clinician's perspective has value in framing an experience within the context of what is usual for a group of individuals, and the population perspective provides inputs as to how society may use limited resources. However, we conclude that a more prominent role for the patient's QOL perspective is needed.

Preoperative Prediction of the Risk of Pulmonary Complications After Esophagectomy for Cancer—Ferguson MK, Durkin AE. J Thorac Cardiovasc Surg 2002 Apr;123(4):661-669.

OBJECTIVES: Pulmonary complication is a frequent morbid event after esophagectomy for cancer. Its prediction may help select patients for preoperative rehabilitation. METHODS: We performed a retrospective

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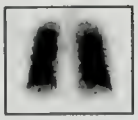

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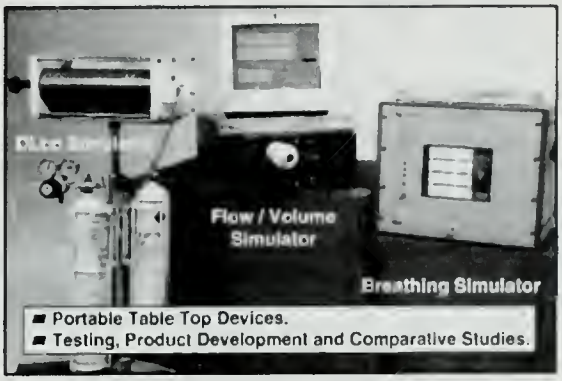
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review of 292 patients (231 men and 61 women; mean age, 60.1 years) who underwent esophagectomy for cancer between 1980 and 2000. Data were analyzed to identify factors associated with the development of pulmonary complications (reintubation for isolated respiratory failure and pneumonia). A scoring system was developed, and its ability to predict complications was assessed. RESULTS: Resection was performed for squamous cancer (n = 100), adenocarcinoma (n = 186), and other histologic types (n = 6) in patients with stages 0 or I (n = 53), II (n = 94), III (n = 114), and IV (n = 23) disease. Pulmonary complications, which developed in 78 (27%) patients, were associated with a 4.5-fold increase in operative mortality (7%-32%). Multivariable analysis identified independent predictors of pulmonary complications to be patient age (odds ratio [OR], 1.31; 95% confidence interval [CI], 0.99-1.74; p =0.059), percentage forced expiratory volume in 1 second (OR, 1.21; 95% CI, 1.07-1.38; p =0.003), and possibly performance status (OR, 1.48; 95% CI, 0.88-2.50; p =0.14). A scoring system using these 3 covariates was developed, which predicted incremental risk of pulmonary complications (p =0.013). The incremental risks of cardiovascular and overall cardiopulmonary complications were also predicted with this scoring system (p <0.01 for each). CONCLUSIONS: A scoring system using patient age, spirometry, and performance status helps predict the likelihood of pulmonary and cardiovascular complications after esophagectomy and can help select patients who may benefit from preoperative cardiopulmonary rehabilitation.

Epidemiology of Obstructive Sleep Apnea: A Population Health Perspective—Young T, Peppard PE, Gottlieb DJ. Am J Respir Crit Care Med 2002 May 1;165(9):1217-1239.

Population-based epidemiologic studies have uncovered the high prevalence and wide severity spectrum of undiagnosed obstructive sleep apnea, and have consistently found that even mild obstructive sleep apnea is associated with significant morbidity. Evidence from methodologically strong cohort studies indicates that undiagnosed obstructive sleep apnea, with or without symptoms, is independently associated with increased likelihood of hypertension, cardiovascular disease, stroke, daytime sleepiness, motor vehicle accidents, and diminished quality of life. Strategies to decrease the high prevalence and associated morbidity of obstructive sleep apnea are critically needed. The reduction or elimination of risk factors through public health initiatives with clinical support holds promise. Potentially modifiable risk factors considered in this review include overweight and obesity, alcohol, smoking, nasal congestion, and estrogen depletion in menopause. Data suggest that obstructive sleep apnea is associated with all these factors, but at present the only intervention strategy supported with adequate evidence is weight loss. A focus on weight control is especially important given the expanding epidemic of overweight and obesity in the United States. Primary care providers will be central to clinical approaches for addressing the burden and the development of cost-effective case-finding strategies and feasible treatment for mild obstructive sleep apnea warrants high priority.

Manual Aspiration Versus Chest Tube Drainage in First Episodes of Primary Spontaneous Pneumothorax: A Multicenter, Prospective, Randomized Pilot Study—Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraeten A. Am J Respir Crit Care Med 2002 May 1;165(9):1240-1244.

Although there is no agreement on the optimal treatment of patients presenting with a first episode of primary spontaneous pneumothorax, the majority of physicians prefer chest tube drainage for air evacuation. Manual aspiration of air has been proposed by some, but lack of sound comparative data and safety data has limited its use. In this first randomized, prospective, multicenter pilot study, 60 patients with a first episode of primary spontaneous pneumothorax were randomly allocated to manual aspiration (n = 27) or chest tube drainage (n = 33). Immediate success was obtained in 16 out of 27 (59.3%) in the manual aspiration group, and in 21 out of 33 (63.6%) in the chest tube drainage group (p = 0.9). One-week success rates were 25 out of 27 (93%) in the intention-to-treat manual aspiration group and 28 out of 33 (85%) in the chest tube drainage group (p = 0.4). Fourteen of 27 manual aspiration patients (52%) were hospitalized, versus 100% of the chest tube drainage patients (p < 0.0001). Recurrence rates with at least 1-year follow-up were 7 out of 26 (26%) in the manual aspiration group, and 9 out of 33 (27.3%) in the chest tube drainage group (p = 0.9). There were no complications associated with manual aspiration. Although statistical power is insufficient to formally confirm therapeutic equality, this pilot study suggests that in first episodes of primary spontaneous pneumothorax, manual aspiration seems equally effective as chest tube drainage and is safe, well tolerated, and feasible as an outpatient procedure in the majority of patients.

Dyspnea and Decreased Variability of Breathing in Patients with Restrictive Lung Disease—Brack T, Jubran A, Tobin MJ. Am J Respir Crit Care Med 2002 May 1;165(9):1260-1264.

Patients with restrictive lung disease are typically dyspneic and have an increase in overall respiratory center drive, as a result of increased lung elasticity. When we subjected healthy volunteers to external elastic loads, their variability of breathing was lessened. Accordingly, we hypothesized that patients with restrictive lung disease display decreased variability of breathing and, also, that decreased variability of breathing is related to dyspnea. Breathing pattern was measured nonobtrusively over 1 hour in 10 patients with restrictive lung disease and in 7 healthy subjects. On a separate occasion, dyspnea was measured while all subjects copied different tidal volumes and frequencies. Compared with healthy subjects, the random fraction of breath variability was reduced in patients with restrictive lung disease: 27 times for expiratory time, 12 times for tidal volume, and 6 times for inspiratory time ($p < 0.01$ in each instance). Conversely, the nonrandom, correlated fraction for tidal volume was increased almost 3-fold in the patients ($p < 0.01$). Small variations from average resting tidal volume caused marked increases in dyspnea in patients, and the relationship was parabolic ($r^2 = 0.97$; $p < 0.001$). In conclusion, patients with restrictive lung disease adopt a tightly constrained breathing pattern, probably as a strategy for avoiding dyspnea.

ARDSNet Lower Tidal Volume Ventilatory Strategy May Generate Intrinsic Positive End-Expiratory Pressure in Patients with Acute Respiratory Distress Syndrome—de Durante G, del Turco M, Rustichini L, Cosimini P, Giunta F, Hudson LD, et al. Am J Respir Crit Care Med 2002 May 1;165(9):1271-1274.

The ARDSNet trial revealed that the use of a smaller tidal volume (V_T) reduced mortality by 22%. However, three earlier studies that lowered V_T did not find a decrease in mortality. We tested the hypothesis that the increased respiratory rate used in the ARDSNet lower V_T strategy might have led to intrinsic positive end-expiratory pressure ($PEEP_i$), raising total PEEP ($PEEP_{total}$). Ten patients with acute respiratory distress syndrome (ARDS) were ventilated using the ARDSNet lower V_T protocol. Respiratory rate was then reduced (10-15 breaths/minute) to obtain a V_T of 12 mL/kg (ARDSNet traditional V_T). PEEP on the ventilator ($PEEP_{nominal}$: 10.1 ± 0.7 cm H_2O), F_{IO_2} (0.7 ± 0.1), and minute ventilation $\dot{V}_E$: 12.4 ± 1.7 L/minute) were set using the ARDSNet protocol and maintained constant during the two ventilatory strategies. Values of airway pressure at end-expiration of a regular breath ($PEEP_{external}$) and 3-5 seconds after the onset of an end-expiratory occlusion ($PEEP_{total}$) were measured. $PEEP_i$ was calculated by subtracting $PEEP_{external}$ from $PEEP_{total}$. $PEEP_{total}$ and $PEEP_i$ were, respectively, 16.3 ± 2.9 and 5.8 ± 3.0 cm H_2O during the lower V_T strategy and 11.7 ± 0.9 and 1.4 ± 1.0 cm H_2O during the traditional V_T strategy ($p < 0.01$). The reduced mortality observed with the ARDSNet strategy may have been due to the protective effect of a higher $PEEP_{total}$.

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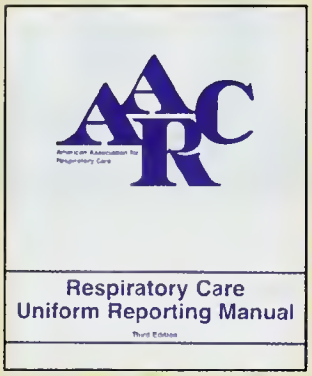

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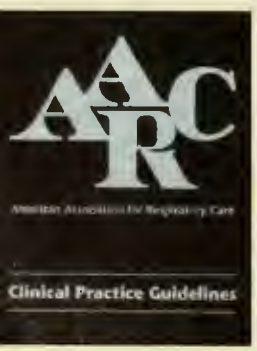

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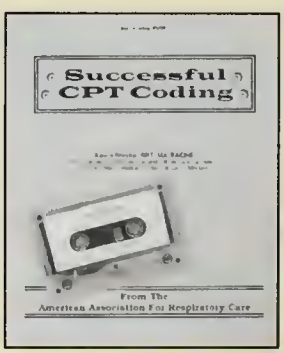

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Infants with Flow Limitation at 4 Weeks: Outcome at 6 and 11 Years—Turner SW, Palmer LJ, Rye PJ, Gibson NA, Judge PK, Young S, et al. Am J Respir Crit Care Med 2002 May 1;165(9):1294-1298.

Within a longitudinal study of lung function in 243 infants, we identified a group of 23 individuals with flow limitation in tidal expiration. In infancy, flow-limited children have reduced lung function and increased airway responsiveness (AR), and at 2 years of age they are diagnosed with asthma more frequently. We hypothesized that these observations would persist throughout childhood. Data from ages 3 to 11 years were analyzed. Only at 4 years of age did the flow-limited group have increased wheeze compared with other cohort members (odds ratio, 4.25; 95% confidence interval [CI], 1.11 to 16.2; p = 0.04; n = 114). At 6 years of age, 117 cohort members were seen. The flow-limited group (n = 14) had greater AR (p = 0.009) and reduced mean FEV_1 (131 mL; 95% CI, 16 to 246; p = 0.03) and FEF_{25-75} (0.28 L/second; 95% CI, 0.05 to 0.52; p = 0.02). At 11 years of age, 183 children were seen and the flow-limited group (n = 18) had greater AR (p = 0.02) and a trend toward reduced mean FEF_{25-75} (0.24 L/second; 95% CI, -0.02 to 0.49; p = 0.08). Atopy and parental asthma were not increased in the flow-limited group. We suggest that the physiologic abnormality that causes flow limitation in early infancy may identify an at-risk group, different from asthma, who have reduced lung function and increased airway responsiveness in later life.

Prospective Study of Diet and Decline in Lung Function in a General Population—McKeever TM, Scrivener S, Broadfield E, Jones Z, Britton J, Lewis SA. Am J Respir Crit Care Med 2002 May 1;165(9):1299-1303.

We have investigated the relationship between decline in lung function and dietary intakes of magnesium, vitamin C, and other antioxidant vitamins in a general population cohort in Nottingham, United Kingdom. In 1991, we measured dietary intake by semiquantitative food frequency questionnaire, forced expiratory volume in 1 second (FEV_1), and respiratory symptoms in a cross-sectional survey of 2,633 adults aged 18-70. Nine years later we repeated these measures in 1,346 of these individuals. In cross-sectional analyses, after adjustment for smoking and other confounders, higher intakes of vitamin C and magnesium, but not vitamins A or E, were associated with higher levels of FEV_1 in both 1991 and 2000. In longitudinal analysis with adjustment for confounders, decline in FEV_1 between 1991 and 2000 was lower amongst those with higher average vitamin C intake by 50.8 mL (95% confidence interval, 3.8-97.9) per 100 mg of vitamin C per day, but was unrelated to magnesium intake. There was no relationship between decline in FEV_1 and intake of vitamins A or E. This study suggests that a high dietary intake of vitamin C, or of foods rich in this vitamin, may reduce the rate of loss of lung function in adults and thereby help to prevent chronic obstructive pulmonary disease.

The Best Peak Expiratory Flow Is Flow-Limited and Effort-Independent in Normal Subjects—Tantucci C, Duguet A, Giampiccolo P, Similowski T, Zelter M, Derenne JP. Am J Respir Crit Care Med 2002 May 1;165(9):1304-1308.

Recently, it has been suggested that peak expiratory flow (PEF) may be determined by the wave speed flow-limiting mechanism. In six normal male subjects (age = 33 ± 8 years) performing expiratory forced vital capacity (FVC) maneuvers, a negative expiratory pressure (NEP) of -10 cm H_2O was randomly applied at the beginning of maximal expiration to assess changes in PEF as compared with baseline. During FVC maneuvers, the expiratory effort was measured by changes in esophageal pressure (Pes), as either peak expiratory Pes-Pes at end expiratory lung volume (ΔPes_{peak}) or maximal rate of rise of Pes ($dPes/dt_{max}$). In each experimental condition, at least three FVC maneuvers with comparable expiratory effort were selected for analysis for each subject. With similar ΔPes_{peak} (107.2 ± 34.9 versus 111.7 ± 40.5 cm H_2O) and $dPes/dt_{max}$ (1181 ± 518 versus 1177 ± 546 cm H_2O/second) PEF amounted to 10.84 ± 1.08 L/second and to 10.82 ± 1.03 L/second with and without NEP, respectively. These data show that PEF obtained by normal subjects to the best of their abilities (best PEF) does not increase with NEP and indicate that the best PEF is a flow-limited and effort-independent parameter, reflecting only lung and airways mechanics as the other subsequent maximal expiratory flows achieved during the FVC maneuver.

The Utility of Albuterol Nebulized with Heliox During Acute Asthma Exacerbations—Kress JP, Noth I, Gehlbach BK, Barman N, Pohlman AS, Miller A, et al. Am J Respir Crit Care Med 2002 May 1;165(9):1317-1321.

Heliox improves lung deposition of inhaled particles when compared with air or oxygen inhalation. We studied the spirometric effects of albuterol nebulized with heliox during emergency room visits for asthma exacerbations. Forty-five patients were randomized to receive albuterol nebulized with oxygen (control) versus heliox (n = 22 control and 23 heliox subjects). At baseline, demographics, outpatient asthma medications, vital signs, oxygen saturation, and forced expiratory volume in one second were not different between the two groups. Three consecutive albuterol treatments were given to each group. The heliox group had a significantly higher heart rate after albuterol nebulization compared with the control group. Following albuterol Treatment 1, the median change in forced expiratory volume in one second was 14.6% in the control group and 32.4% in the heliox group (p = 0.007). After Treatment 2, the results were 22.7% versus 51.5%, respectively (p = 0.007). After Treatment 3, the results were 26.6% versus 65.1%, respectively (p = 0.016). We conclude that during acute asthma exacerbations, albuterol nebulized with heliox leads to a more significant improvement in spirometry when compared with albuterol nebulized with oxygen. This is likely due to the low-density gas improving albuterol deposition in the distal airways.

Organizational and Environmental Factors that Affect Worker Health and Safety and Patient Outcomes—Lundstrom T, Pugliese G, Bartley J, Cox J, Guither C. Am J Infect Control 2002 Apr;30(2):93-106.

This article reviews organizational factors that influence the satisfaction, health, safety, and well-being of health care workers and ultimately, the satisfaction, safety, and quality of care for patients. The impact of the work environment on working conditions and the effects on health care workers and patients are also addressed. Studies focusing on worker health and safety concerns affected by the organization and the physical work environment provide evidence of direct positive and/or adverse effects on performance and suggest indirect effects on the quality of patient care. The strongest links between worker and patient outcomes are demonstrated in literature on nosocomial transmission of infections. Transmission of infections from worker to patient and from patient to patient via health care worker has been well documented in clinical studies. Literature on outbreaks of infectious diseases in health care settings has linked the physical environment with adverse patient and worker outcomes. An increasing number of studies are looking at the relationship between improvement in organizational factors and measurable and positive change in patient outcomes. Characteristics of selected magnet hospitals are reviewed as one model for improving patient and worker outcomes.

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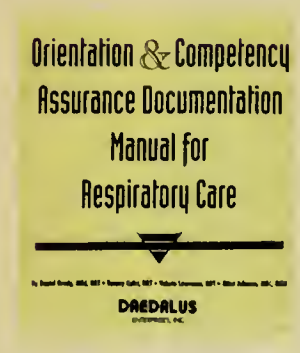

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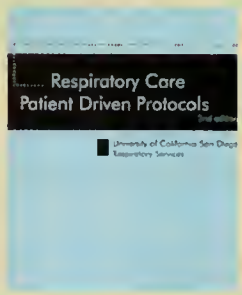

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Part I of Two Special Issues

Liquid Nebulization: Emerging Technologies

Containing the papers and discussions from the 30th RESPIRATORY CARE Journal Conference

Presented under the auspices of the American Respiratory Care Foundation.

Supported in part by unrestricted educational grants from Aerogen, Allegiance Healthcare, AstraZeneca, Boehringer Ingelheim, DHD Healthcare, Monaghan Trudell, Salter Labs, and VIASYS Healthcare

Conference faculty members—front row, from left: Joseph L Rau PhD RRT FAARC, Dean R Hess PhD RRT FAARC, Myrna B Dolovich PEng, Neil R MacIntyre MD FAARC, Gerald C Smaldone MD PhD, Thomas G O'Riordan MD. Back row, from left: Alessandro Gomez PhD, Rajiv Dhand MD, Patrick J Dunne MEd RRT FAARC, Peter W Barry MD, Bruce K Rubin MD MEng FAARC, David E Geller MD, John H Dennis PhD MSc. Not pictured: Robert J Meyer MD.

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Foreword

Liquid Nebulization: Emerging Technologies

Delivery of aerosolized medications into the lungs is becoming increasingly important for two reasons. First, medications aimed at lung diseases often have a higher therapeutic index when delivered directly into the lung. Although bronchodilators are currently the most common aerosolized medication, many new classes of drugs (eg, antibiotics, antioxidants, and anti-inflammatory agents) are being developed that lend themselves to this mode of delivery. Second, medications aimed at systemic illnesses (eg, insulin, human growth factor, and calcitonin) are also being administered as aerosols and are being shown to have reliable systemic delivery through alveolar-capillary transport.

Current aerosol delivery systems may not be adequate for these new applications. This is because current systems can be very inefficient, and aerosol delivery can be heavily dependent on a variety of sometimes difficult-to-control factors, including breathing pattern, airway geometry, humidity, aerosol particle size/shape/velocity, and device performance characteristics. Under optimal conditions lung deposition may approach 50% with these systems. Unfortunately, however, all too often in clinical practice, lung deposition is considerably less than that, especially in pediatric patients and uncooperative adults. Efficient delivery can be further compromised by the presence of an artificial airway. Though these inefficiencies are clinically manageable for inexpensive drugs such as bronchodilators (just give more drug), they are unacceptable when considering aerosol delivery of potentially very expensive newer medications.

An additional problem in current aerosol delivery is specific location targeting. Many drugs are more effective if they are placed in specific regions within the lung. For example, drugs designed for parenchymal diseases might be most effective if delivered to alveolar regions. Conversely, drugs designed for airway disease might be most effective if delivered to proximal airways. Though some targeting can be accomplished by particle size and velocity manipulations (smaller, slower particles deposit more distally), current technology has limited targeting capabilities.

Some fascinating new approaches to aerosol delivery are on the horizon. These include novel device characteristics, new drug formulations, clever patient interfaces, and approaches that generate the aerosol within specific regions of the lung. The purpose of the 30th RESPIRATORY CARE Journal Conference was to gather recognized experts in nebulization and aerosol delivery and address these developments in several ways. The program was structured in 3 parts: (1) a review of basic nebulization principles and limitations of current systems, (2) discussions about how assessments of future systems should be done and what would be the barriers to implementation, and (3) specific analyses of the concepts underlying new devices and interfaces.

This and the next issue of RESPIRATORY CARE provide the proceedings of the conference on Liquid Nebulization: Emerging Technologies. We hope that these articles will increase understanding of aerosol delivery and provide insight as to how newer design principles can improve upon this very useful form of drug delivery.

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Design Principles of Liquid Nebulization Devices Currently in Use

Joseph L Rau PhD RRT FAARC

Introduction
Jet Nebulizers
Principle of Operation
Variables of Nebulizer Performance
Advantages and Disadvantages of Jet Nebulizers
Design Variations in Traditional Jet Nebulizers
Ultrasonic Nebulizers
Description and Basic Function
Physics of Ultrasonic Nebulization
Theory of Aerosol Production
Comparison of Ultrasonic and Jet Nebulizers
Advantages and Disadvantages of Ultrasonic Nebulizers
Summary

Liquid nebulization is a common method of medical aerosol generation. Nebulizers are of 2 types: jet (or pneumatic) small-volume nebulizer, and ultrasonic nebulizer. Jet nebulizers are based on the venturi principle, whereas ultrasonic nebulizers use the converse piezoelectric effect to convert alternating current to high-frequency acoustic energy. Important variables for both types of nebulizer are treatment time required, particle size produced, and aerosol drug output. There are several advantages to jet nebulization, including that effective use requires only simple, tidal breathing, and that dose modification and dose compounding are possible. Disadvantages include the length of treatment time and equipment size. Design modifications to the constant-output nebulizer have resulted in breath-enhanced, open-vent nebulizers such as the Pari LC Plus and the dosimetric AeroEclipse. Ultrasonic nebulizers generally have a higher output rate than jet nebulizers, but a larger average particle size. Ultrasonic nebulizers can also substantially increase reservoir solution temperature, the opposite of jet nebulizer cooling. Drug concentration in the reservoir does not increase with ultrasonic nebulization, as it does with jet nebulization. Ultrasonic nebulizers have the same advantages as jet nebulizers. Ultrasonic nebulizers are more expensive and fragile than jet nebulizers, may cause drug degradation, and do not nebulize suspensions well. Neither type of nebulizer meets the criteria for an ideal inhaler: efficient and quick dose delivery with reproducibility, cost-effectiveness, and no ambient contamination by lost aerosol. *Key words: nebulization, jet nebulizer, aerosol, ultrasonic.* [Respir Care 2002;47(11):1257–1275]

Introduction

The term "nebulizer" derives from the Latin "nebula," meaning "mist," and reportedly was first used in 1872, followed by an 1874 definition as "an instrument for converting a liquid into a fine spray, especially for medical purposes."[1] The appealing logic of creating a vapor or aerosol for the inhalation treatment of lung disease is at least as old as written records of medicine. The Ayurvedic tradition of medicine in India, which dates back perhaps

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Joseph L Rau PhD RRT FAARC presented a version of this report at the 30th Respiratory Care Journal Conference, Liquid Nebulization: Emerging Technologies, held June 28–30, 2002, in Montréal, Québec, Canada.

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4,000 years or more, used inhaled substances for managing asthma.[2] Although inhalation devices were described in the 19th century, the modern precursors of small-volume nebulizer devices appeared with the glass and handbulb "atomizers" introduced for asthma treatment in the 1930s, such as the DeVilbiss No. 40 glass nebulizer.[1] The Collison nebulizer became available in the late 1940s; it used a baffle to filter out large particles, thus distinguishing a "nebulizer" from an "atomizer."[3] The Wright nebulizer, which appeared in the 1950s, was engineered from ebonite and perspex; it was much more compact than the Collison and more closely resembled today's pneumatically powered nebulizers.[4] A different method of creating liquid aerosols, the ultrasonic nebulizer, was introduced in the 1960s. It relies on high-frequency sound waves to aerosolize the solution. Today the term "nebulizer," as used clinically in respiratory care, encompasses both gas-powered jet nebulizers and ultrasonic nebulizers. This review considers the physical principles, designs, advantages, disadvantages, and factors affecting performance of jet and ultrasonic nebulizers that are in current clinical use.

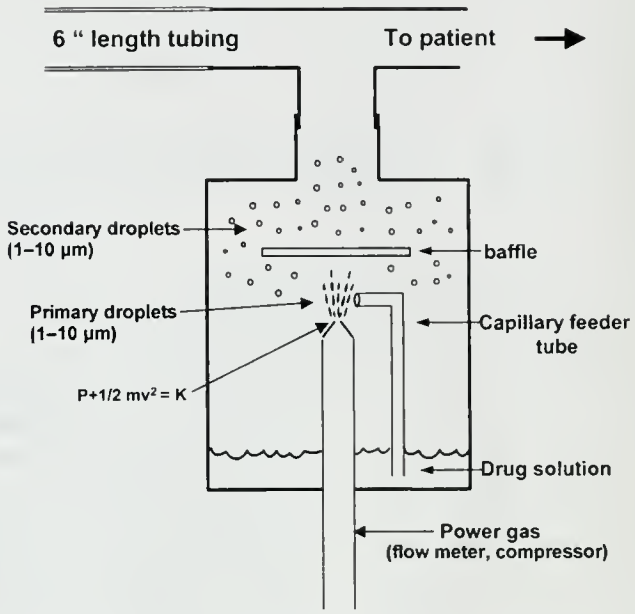

Fig. 1. The major elements of a jet (pneumatically powered) small-volume nebulizer. m = mass. v = velocity. P = pressure. K = constant.

Jet Nebulizers

Principle of Operation

Small-volume jet (pneumatic) nebulizers are 2-fluid atomizers. The basic principle of operation involves compressed gas directed through a narrow orifice, with entrainment of liquid through one or more capillary feeder tubes. The narrow-orifice gas nozzle has traditionally been termed a "venturi," with liquid entrainment based on the Bernoulli principle. In laminar flow, and keeping height constant, Bernoulli's equation[5] for an incompressible fluid states:

$$\tfrac{1}{2}\,mv^2 + P = \text{constant}$$

in which m = mass, v = velocity, P = pressure, and $\tfrac{1}{2}\,mv^2$ represents kinetic energy. For a gas in laminar flow through a tubing system, an increase in velocity, such as can occur at a restriction in the tubing, leads to a decrease in the lateral pressure. If kinetic energy increases, pressure energy must decrease, based on conservation of mass and energy. A "venturi" is based on Bernoulli's equation and uses the pressure drop to entrain a second fluid. The lower pressure causes drug solution to be drawn up to the gas jet through capillary or feeder tubes that lead down to the liquid reservoir. The entrainment is also attributed to momentum transfer between the power-gas molecules and air or liquid in the feeder tubes.[6] The high-velocity gas meeting the liquid causes primary generation of large droplets, typically 40–60 μm, but with a possible range of 15 to > 500 μm.[7,8] Droplets produced by primary generation are impacted onto baffles within the nebulizer, producing a secondary generation of aerosol with particles of 1–10 μm, with typical sizes of 4.0 and 5.0 μm.[7] During that second stage of aerosol generation the larger particles are baffled, coalesce, and drain back into the reservoir (Figure 1).

Aerosol droplet size depends on the geometry of the nozzle and baffles, nozzle diameter, gas velocity, mass flow of gas, and the physical constants of the power-gas and drug solution. Jet nebulizers produce a range of particle sizes, which is a distribution termed "polydisperse" or "heterodisperse," in contrast with "monodisperse" aerosols.[9] The mass median aerodynamic diameter (MMAD) is the median droplet size of the cloud of aerosol particles. Particles of 1–5 μm diameter have a higher probability of reaching the lower respiratory tract than do larger particles.[9] However, there is a trade-off between particle size and drug amount. With spherical particles, the mass of drug varies directly as the third power of the particle radius. An increase in particle size gives an exponential increase in drug mass, but the converse is also true. With aqueous solutions the extremely large surface area created by aerosol particles and a dry power-gas cause considerable evaporation and substantial cooling of the nebulizer, because of latent heat of vaporization, to approximately 10° C below ambient temperature, within minutes.[10] Higher power-gas flows can increase the amount of temperature drop in some nebulizers.[11] The amount of temperature drop differs among nebulizer brands,[11] and the amount of temperature drop is less with a partially humidified power-

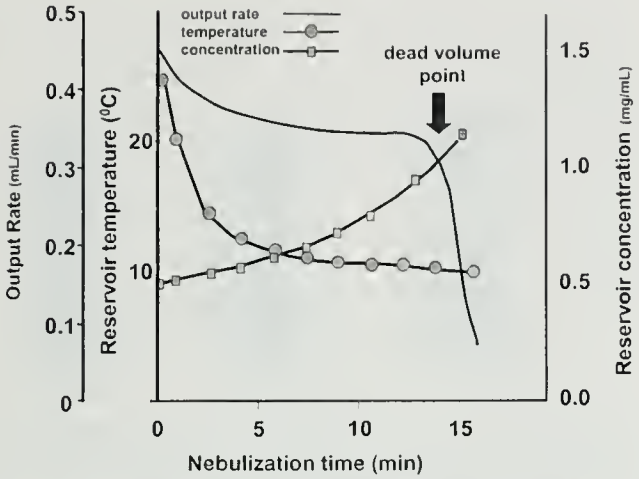

Fig. 2. Functioning of a small-volume jet nebulizer with respect to output rate, solution temperature, and concentration of solute in the solution during nebulization. The data are hypothetical and not based on actual measurements of a particular brand of nebulizer.

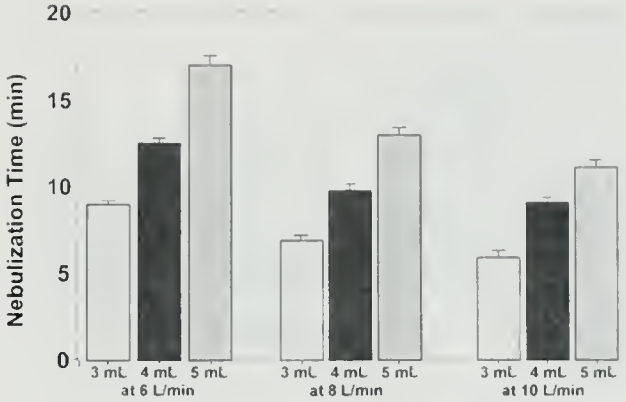

Fig. 3. Nebulization time is a function of both the power-gas flow rate and the fill volume. Lower flow rates and higher fill volumes increase the nebulization time. The graph shows pooled data from 17 nebulizers. (From Reference 17, with permission.)

gas, such as from a compressor, than with a drier gas, such as from a cylinder or wall outlet.[12] The evaporation also increases the solution's drug concentration during the time of operation.[10,13,14] Dennis et al found an increase from 1% to 3% using 5 mL of a solution of sodium fluoride in a Wright nebulizer—a 200% increase in concentration.[15] Concentration increases ranging from 5% to over 37% have been found with other jet nebulizers, using albuterol solution.[16] Figure 2 shows a generic illustration of output rate, temperature, and solution concentration for a typical small-volume jet nebulizer. In the first minutes the output rate falls as the solution temperature drops and viscosity and surface tension increase.[10] A plateau is then reached in both output and temperature, until a point at which output decreases precipitately; this is usually the point at which the level of liquid in the reservoir falls below the bottom of the capillary feeder tube. At that point, gas is drawn up with the liquid, the nebulizer begins to sputter, and aerosol creation is intermittent. Tapping the nebulizer can cause baffled droplets to coalesce, run down the walls of the reservoir, increase the solution level, and temporarily restore aerosolization. Ultimately nebulization ceases, although the nebulizer contains some residual solution on the apparatus walls, baffles, and at the bottom of the reservoir chamber. The amount of that remaining liquid is termed the "dead volume," which in most small-volume nebulizers is approximately 1 mL.[10] The fact that most nebulizers cannot aerosolize well below 1 mL is the reason that a bland diluent of saline or water is added to a 0.5 mL drug dose: for example, albuterol from a multi-use bottle of 0.5% solution. Addition of the diluent is not to weaken the drug solution, but is in fact needed if any aerosol is to be produced, and increases the amount of drug emitted by the nebulizer.[17]

Variables of Nebulizer Performance

Several variables describe the nebulizer performance, including the time required for nebulization, droplet size produced, and drug output.

Nebulization Time. The time required is directly proportional to the volume of solution placed in the reservoir and inversely proportional to the power-gas flow (Fig. 3).[11,17]

Determination of nebulization time in studies differs because it is difficult to decide when aerosolization has ceased. The nebulization time depends on how the end point of nebulization is defined. Kradjan and Lakshminarayan defined 3 possible end points for nebulization: sputtering time, total time, and clinical time.[18] Sputtering is the point when aerosolization becomes erratic, as noted by seeing and hearing. Total time is when production of aerosol ceases. Clinical time is between sputtering and total time, and approximates the point when a patient or therapist typically stops a treatment. With a 3 mL volume, averaged over 5 nebulizer brands, the sputtering, clinical, and total times were measured as 7.3, 9.9, and 12.8 min, respectively, by Kradjan and Lakshminarayan.[18] Nebulization time may also be defined as the point 30 seconds after sputter, with or without tapping, although this can introduce greater subjectivity in the measurement. Regardless of the end point chosen, it is important that studies define the end point clearly, in order to allow comparisons.

There is evidence to suggest that nebulization time varies directly with the viscosity of solutions. Antibiotic solutions can be more viscous than aqueous bronchodilator solutions and can require more powerful compressors (ie, higher power-gas flows) to keep nebulization times from being prolonged. Hess et al found that the average nebulization time pooled for 17 nebulizers, using albuterol,

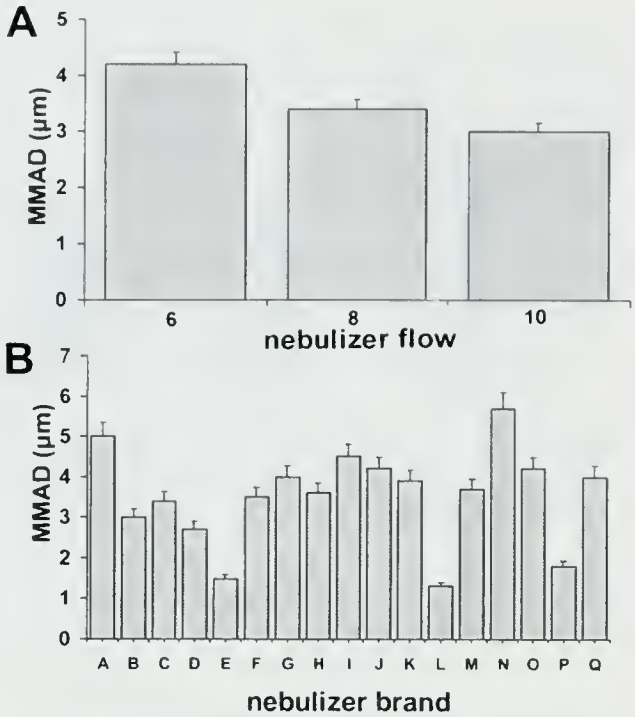

Fig. 4. A. Effect of power-gas flow rate on mass median aerodynamic diameter (MMAD), with smaller particle sizes at higher power-gas flow rates. The graph shows pooled data from 17 nebulizers. B. MMAD for 17 nebulizer brands, pooled for all power-gas flow rate settings. (From Reference 17, with permission.)

with 4 mL volume and 6 L/min power-gas flow, was approximately 13 min.[17] Newman et al investigated nebulized gentamicin solution with 4 different nebulizers and found that 4 mL (160 mg) at 6 L/min power-gas flow required between 17 and 25 min.[19] The approximate average time pooled for the 4 nebulizers was 20 min. That study recommended flows of 10–12 L/min or a high-flow compressor for nebulization of antibiotic solutions.

Particle Size. Particle size is a major factor influencing the probability of drug particles reaching the various levels of airway generation.[20] Particle size produced by a small-volume jet nebulizer is inversely proportional to power-gas flow (or compressor pressure). Hess et al found that the MMAD varied inversely with power-gas flow rates between 6 and 10 L/min (Fig. 4A).[17] In that study the percentage of 1–5 μm particles increased with higher power-gas flow rates. Similar data were reported from the United Kingdom by Clay et al for 4 disposable jet nebulizers.[21] Increasing the power-gas flow rate produced smaller particles and reduced nebulization time. Particle size is also affected by the physical characteristics of the drug solution, such as surface tension and viscosity.[19,22] Hess et al found that the MMAD produced by 17 nebulizers differed significantly (see Fig. 4B),[17] and the percentage of 1–5 μm particles ranged from slightly over 30% to 60%. Clay et al found an inverse relationship between the MMAD and the geometric standard deviation, indicating that the MMAD was smaller but the aerosol was more heterodisperse at higher flow rates.[21]

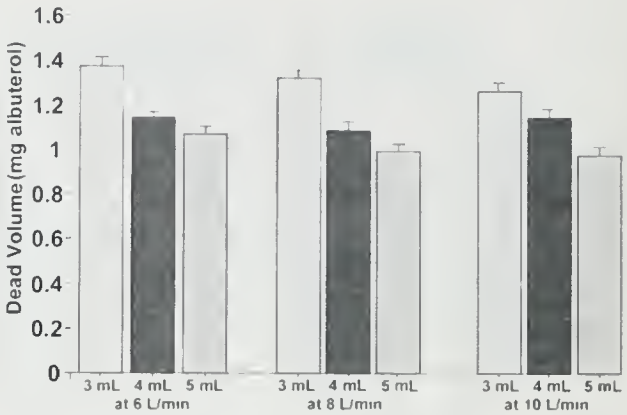

Fig. 5. Effect of power-gas flow rate (6, 8, or 10 L/min) and fill volume (3, 4, or 5 mL) on amount of drug remaining in the dead volume. The graph shows pooled data from 17 nebulizers. (From Reference 17, with permission.)

Aerosol Drug Output. The primary factors affecting the amount of aerosolized drug released from a jet nebulizer are the fill volume and, secondarily, the type of nebulizer. Increasing the fill volume results in lower concentrations of drug remaining in the dead volume of the nebulizer, when nebulization ceases. This is based on the following relationship:

Dead volume drug (mg) = dead volume (mL)

× concentration (mg/mL)

With a theoretical dead volume of 1.0 mL and assuming no increase in concentration of the residual solution due to evaporation, a 2 mL fill volume would leave at least half of the drug in the dead volume. A 4 mL fill volume would only leave a quarter of the drug in the dead volume. In reality, evaporation increases the concentration of the solution remaining in the nebulizer.[15] Increasing the fill volume therefore reduces or "dilutes" the concentration of drug in the dead volume, but also increases nebulization time (Fig. 5).[17] In the case of a 2.5 mg dose of nebulized albuterol, fill volumes of 3, 4, and 5 mL decrease the amount of drug left in the dead volume from approximately 1.4 mg to approximately 1.15 mg and 1.1 mg, respectively.[17] Determination of aerosol output, dead volume, and remaining drug amount depends on the definition of "end of nebulization."

The type of nebulizer can also affect the amount of drug available for inhalation. Devadason et al compared 4 neb-

ulizer systems (Acorn, Acorn plus Mizer, Ventstream, and Pari LC) and found significant differences in the delivery of albuterol to inspiratory filters, ranging from 9.35% to 19% of the nominal dose.[23] Barry et al compared outputs of a nebulized corticosteroid (budesonide) from the Ventstream, the Pari LC Plus, and the Pari LC Star, using the compressors specified for each. The nebulizers differed in both the rate of output (7.3–14.5 μg/min) and the total output of drug collected on inspiratory filters (32.3–91.9 μg), using simulated conditions of breathing.[24]

The physical properties of the power-gas and the solution to be nebulized also affect nebulizer output. Substituting heliox for air decreased particle size and inhaled drug mass significantly, using albuterol.[25] Nebulized albuterol availability was greater from a solution containing the preservative benzalkonium chloride, because of the lower surface tension produced by the preservative (35.0 ± 0.5 millinewtons per meter with preservative vs 70.5 ± 0.5 millinewtons per meter without).[22] The foaming seen with the lower surface tension from the preservative resulted in more return of liquid to the reservoir and a smaller dead volume than with the preservative-free solution, with which large droplets adhered to the nebulizer walls and increased the dead volume. Coates et al also found that nebulizer output of aerosolized tobramycin was greater with the addition of albuterol containing benzalkonium chloride, which lowered the surface tension.[26]

Advantages and Disadvantages of Jet Nebulizers

Table 1 lists the advantages and disadvantages of small-volume jet nebulizers. Chief among the advantages is the simple, tidal breathing pattern used. Complex breathing maneuvers or coordination of breathing with device function is not needed. Drug delivery to the airway is over a period of minutes, with 60–90 breaths, rather than dependent on 1 or 2 carefully timed inspirations with particular flow rates, as with a metered-dose inhaler (MDI) or dry powder inhaler (DPI). A second major advantage is the ability to nebulize various solutions and to modify solution concentration and thereby the amount of drug delivered. Many of the drugs currently used in the United States for inhalation treatment of pulmonary disease are available as nebulizer solutions, and some of these drugs, such as dornase alfa (Pulmozyme) and inhaled tobramycin (TOBI) are only available in solution form for nebulization. In the United States the use of nebulizers in home therapy is paid for by Medicare, whereas other inhaled drug formulations such as MDI and DPI are not, since drug therapy for nonhospitalized patients is not generally covered by Medicare at this time. This provides an additional economic advantage to nebulized drug therapy for a certain sector of patients.

Table 1. Advantages and Disadvantages of Small-Volume Jet (Pneumatic) Nebulizers

Advantages
· Patient hand-breathing coordination not required
· Effective when used with normal tidal breathing patterns, with no breath-hold
· Effective with low inspiratory flows or volumes
· Ability to aerosolize many drug solutions
· Ability to aerosolize drug mixtures (> 1 drug), assuming suitable testing of drug activity
· Drug concentrations can be modified and high doses are possible
Disadvantages
· Expense of equipment
· Equipment is cumbersome and lacks portability
· Treatment times are lengthy and include set-up and cleaning time
· Variability in performance characteristics
· Possible patient auto-contamination with inadequate cleaning
· Wet, cold spray is produced, which is unpleasant with face-mask delivery
· Need for an external power source (electricity and/or compressed gas)

The chief disadvantages of small-volume jet nebulizers are the size of the equipment (which requires a power source), the inconveniently long treatment time, and the equipment set-up and cleaning. In addition to the lack of portability and slow dosing, disposable jet nebulizers vary in performance among samples of the same brand and among different brands. Hollie et al showed both intranebulizer and internebulizer variability in output and respirable-range output (the "fine particle fraction") for the DeVilbiss 646 jet nebulizer.[27] Alvine et al examined 8 disposable jet nebulizer models, from 6 manufacturers, and found that 4 of the 8 models showed visual signs of malfunction, which included spraying of large, visible droplets, leaking of solution, and air leaks that prevented nebulization completely. Variability of the nebulization rate within a specific model ranged from 57% to 129%.[28] The studies by Hollie et al and Alvine et al attributed the lack of reliability in performance to poor quality control by manufacturers.

Design Variations in Traditional Jet Nebulizers

Although the basic design of jet nebulizers has remained the same over the last 40–50 years, within the last 10 years there have been modifications aimed at reducing device loss and exhaled loss and improving drug availability to the patient. These modifications are in current clinical use, although newer developments in nebulization of liquids are also occurring. Investigational developments are not reviewed herein.

Dennis conceptualized 3 categories of jet nebulizer: constant-output, breath-enhanced, and dosimetric.[13] Figure 6

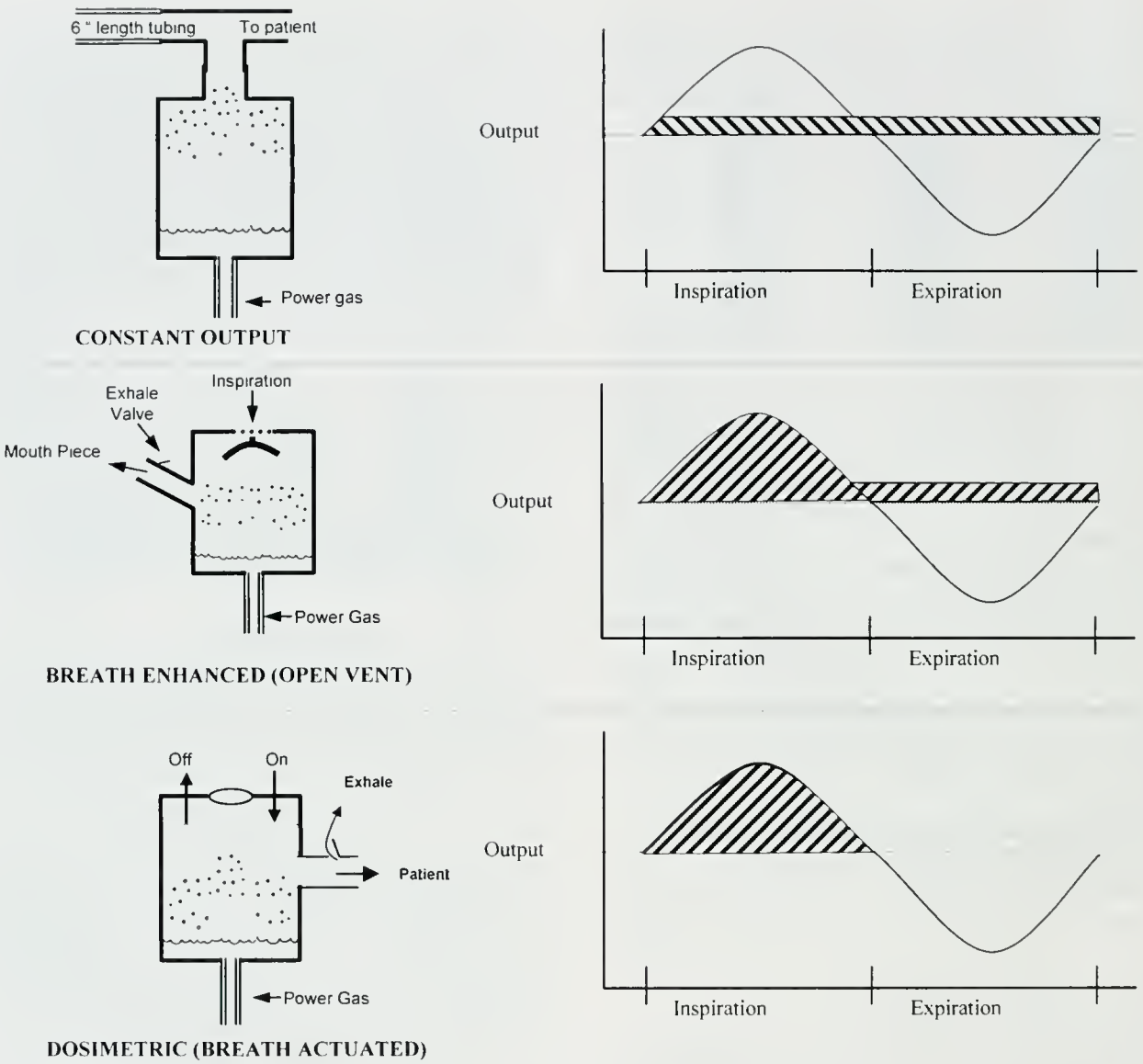

Fig. 6. Jet nebulizer designs. Aerosol generation and delivery are shown for inspiration and expiration, for each type of jet nebulizer: constant-output, breath-enhanced (open-vent), and dosimetric. (Partially based on an illustration from Reference 13.)

shows the basic designs of the 3 types of nebulizer and their aerosol production in relation to the respiratory cycle.

In a constant-output device, aerosol is produced and released constantly, during inspiration and expiration, so aerosol can be lost to the environment whenever inhalation is not occurring. An example is the traditional nebulizer with a mouthpiece connected to a T-piece on the nebulizer cup, such as the Allegiance Airlife Misty-Neb.

A breath-enhanced nebulizer routes inhaled flow through the nebulizer, using a one-way inspiratory valve, thereby increasing the number of aerosol particles in the inspired volume. During exhalation the inspiratory valve closes and aerosol is somewhat contained in the nebulizer, although aerosol generation continues and there is exhaled loss. This design has been referred to as "open vent, breath assisted."[3] Example include the Ventstream and the Pari LC Plus.

A dosimetric nebulizer releases aerosol only during the inhalation cycle.[13] This can be achieved by generating aerosol only during inspiration, using a manual interrupter for the power-gas (as in the Pari LL) or a spring-loaded valve (as in the AeroEclipse) or by containing all aerosol in the device, with no release during expiration (as with the Circulaire). Classifying the Circulaire as a dosimetric device could be questioned because the device nebulizes continuously, but by providing a system of aerosol storage

Table 2. Aerosol Output and Disposition from Jet Nebulizers*

	Total Solute (%)						
	Total Inhaled	Lung	O-P/stomach	Device	Exhaled	Methods	Reference or Source
Constant Output							
In Vivo							
Mini-Neb (8 L/min)	14 (5.1)	12.4 (4.5)	1.5 (0.9)	66.3 (8.6)	19.7 (3.9)	Radiolabel	29
Misty-Neb (7 L/min)	—	8.6 (1.6)	5.6 (3.3)	37 (9)	31.5 (5.8)	Radiolabel	30
Acorn (6 L/min)	9.35 (2.74)	—	—	54.5 (18.2)	—	Insp filter	23
Acorn/Mizer (6 L/min)	13.85 (5.45)	—	—	55.7 (7.0) plus 7.7 (5.5) in Mizer	—	Insp filter	23
In Vitro							
Sidestream, Portaneb	15.3	12.7†	NA	59.3	25.4	Chem tracer	31
Hudson, PulmoAide	22.2	13.4†	NA	55.5	22.3	Chem tracer	31
Cirrus, PulmoAide	18.3	10.6†	NA	62.8	18.9	Chem tracer	31
AeroTee (6 L/min)	32.0 (0.8)	15.2 (0.4)†	NA	NA	—	Spectrophot	32
Breath Enhanced							
In Vivo							
Pari LC, PariBoy	—	12.8 (7.9)	14.2 (7.8)	56.8 (13.1)	16.2 (2.7)	Radiolabel	33
Pari LC Star, Proneb Turbo	—	11.1 (1.7)	13.0 (2.1)	55.2 (3.4)	20.6 (1.2)	Radiolabel	34
Pari IS2 (own compressor)	—	17.1 (8.36)	NA	NA	NA	Radiolabel	35
In Vitro							
Pari LC Plus, PariBoy	25.2	13.8†	—	64.1	10.7	Chem tracer	31
Pari IS2, Pari Master	39.4	33.4†	—	44.7	15.9	Chem tracer	31
Ventstream, CR 50	24.3	17.9†	—	70.9	4.8	Chem tracer	31
Pari LC, InhalerBoy	19.02 (5.78)	NA	—	57.9 (7.4)	—	Insp filter	23
Ventstream (6 L/min)	17.2 (6.83)	NA	—	56.3 (13.5)	—	Insp filter	23
Pari LC Plus, TurboBoy	22.2 (1.8)	15.5‡	—	—	—	Insp filter	24
Ventstream, Portaneb	9.6 (2.4)	8.35‡	—	—	—	Insp filter	24
Pari LC Star, TurboBoy	20.16 (0.4)	15.6‡	—	—	—	Insp filter	24
Dosimetric							
In Vivo							
Circulaire (7 L/min)	—	12.8 (5.1)	1.1 (0.5)	38 (7)	13.9 (9.8)	Radiolabel	30
Pari LL, Pari Boy	—	11.1 (4.0)	13.8 (5.1)	61.9 (6.2)	13.2 (3.0)	Radiolabel	33
In Vitro							
Circulaire (6 L/min)	12.8 (0.4)	3.2 (0.4)†	—	—	—	Spectrophot	32
AeroEclipse (8 L/min)	50.8	41.2	9.6 (calculated)	46.1 (calculated)	3.1	Filter, HPLC	Manufacturer
AeroEclipse (8 L/min)	38.7 (1.34)	34.17 (1.25)	—	51.0 (2.1)	6.6 (3.1)	Spectrophot	Ari et al, 2002§

*Jet nebulizers in 3 categories: constant output, breath enhanced, and dosimetric. In some in vitro studies the lung dose is a calculated amount based on the particle size distribution of the aerosol produced and the measured inhaled mass. The methods column indicates the primary method of drug collection and measurement.
O-P = oropharyngeal. Insp filter = inspiratory filter collection. Chem tracer = chemical tracer. Spectrophot = spectrophotometric. Radiolabel = radiolabeled.
†Mass < 5 μm
‡Mass < 6.1 μm
HPLC = high performance liquid chromatography.
§Unpublished data, Ari et al, Georgia State University, 2002

between breaths, aerosol is released only during inhalation, which is the defining feature of a dosimetric device.[13] Table 2 summarizes studies of aerosol output and disposition for constant-output, open-vent breath-enhanced, and dosimetric nebulizers.

Constant-Output Designs. Most disposable small-volume jet nebulizers typify this functional category. Figure 7 shows data from a study by Lewis and Fleming on drug disposition with a constant-output nebulizer, along with comparison data from an MDI.[29,36] That study found that

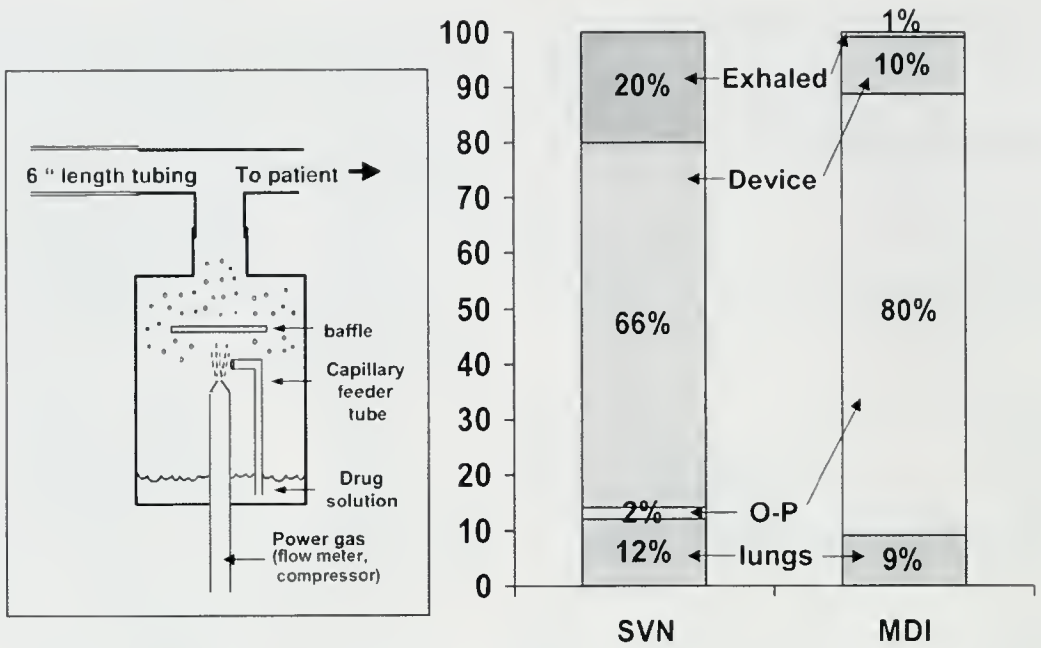

Fig. 7. Disposition of total drug dose with a constant-output jet nebulizer (MiniNeb) versus a metered-dose inhaler (MDI). O-P = oropharyngeal. SVN = small-volume nebulizer. (Modified from Reference 29.)

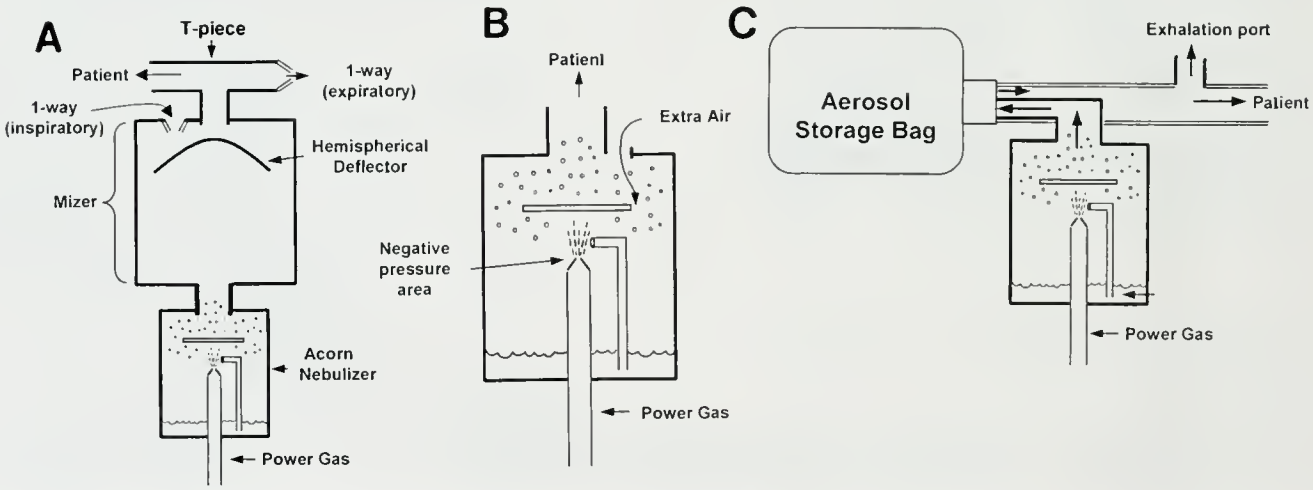

Fig. 8. Three examples of constant-output nebulizers. A. Acorn with Mizer reservoir chamber attached. B. Sidestream with open vent for air entrainment by nebulizer venturi effect. C. AeroTee with aerosol storage bag.

12% of the nominal dose reached the lungs, with 2% to the mouth and stomach, 66% left in the apparatus, and 20% exhaled.[29] Combining the 12% delivered to the lungs with the 2% lost to the oropharynx and stomach gives a total inhaled amount of 14% of the total dose. The dead-volume loss of 66% agrees well with the data of Kradjan and Lakshminarayan, who found that 41–66% of the total dose stayed in the nebulizer under simulated clinical conditions.[18] Constant-output nebulizers have been criticized as more inefficient than other aerosol delivery methods such as the MDI, because of the amount of drug left in the apparatus and exhaled. The traditional jet nebulizer is no more inefficient in delivery of aerosol drug to the airways than other traditional aerosol devices. The pattern of loss, however, differs among jet nebulizers, MDIs, and DPIs. The sizable fraction lost to the nebulizer apparatus is balanced by the 60–80% oropharyngeal and stomach deposition with an MDI or the apparatus and oropharyngeal deposition with a DPI.[36,37] A convincing study by Zainudin et al showed that only about 10% of aerosolized albuterol reaches the lung, regardless of whether a nebulizer, MDI, or DPI is used,[37] though that finding might not apply

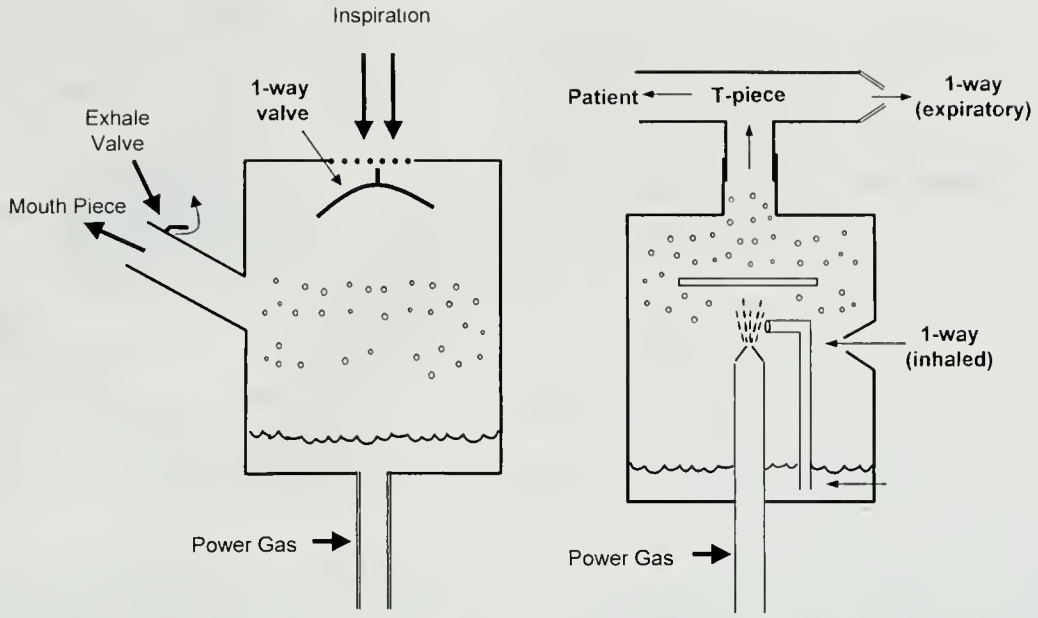

Fig. 9. Two examples of breath-enhanced, open-vent nebulizers. Left: Pari LC Plus. Right: Ventstream.

to newer aerosol devices, some of which are discussed elsewhere in the conference proceedings in this and the following issue of Respiratory Care.

The loss of aerosol from the T-piece of a constant-output nebulizer is visibly obvious during exhalation. Addition of a short length of large-bore tubing to the outlet side of the nebulizer T-piece represented an attempt to reduce exhaled waste and improve the inhaled dose. A 1989 in vitro study by Pisut showed an approximate increase of 20% (from 12% to 14.7%) in inhaled dose with use of large-bore extension tubing on the expiratory side of the T-piece.[38] However a gravimetric method of quantifying drug delivery was used, which may not have accurately reflected drug amounts.[15,39,40]

In a study by Devadason et al, using volunteers and inspiratory filters, the Acorn nebulizer used with the Mizer holding chamber (Fig. 8A) increased the dose of inhaled aerosol from 9.35 ± 2.74% to 13.85 ± 5.45%.[23] A similar difference is found with the AeroTee, which attaches a reservoir bag to the nebulizer outlet (see Fig. 8C). Piper found that the AeroTee delivered a total inhaled dose of 32 ± 0.8% of a nominal 2.5 mg dose of albuterol.[32] The mass of aerosol in the 1–5 μm range was 15.2 ± 0.4%. In the same study a Vixone nebulizer with a T-piece (and no reservoir bag) delivered about 21% of the total dose, of which 9.6% was in the 1–5 μm range.

Another modification to the constant-output nebulizer is the open vent of the Sidestream (see Fig. 8B). The Sidestream's T-piece adaptor has an open vent into the reservoir, which allows continuous air entrainment by the negative pressure of the venturi mechanism.[3] This increases air flow through the chamber and presumably increases drug particles in the inspired gas. However, the same mechanism should apply during exhalation. Nebulization time may be shorter, but inspiratory aerosol emission may be similar to expiratory. This design is considered constant-output, although it is an open vent design as well.[23,31] Using in vitro methodology, Dennis found that the Sidestream emitted a total inhaled dose of 15.3% (458 μL of a 3 mL volume), which does not differ greatly from that of other constant-output nebulizers.[31] The manufacturer claims that the Sidestream produces 80% of particles < 5 μm, compared to approximately 50% from traditional constant-output nebulizers.

Breath-Enhanced, Open Vent Nebulizers. This category is best represented by the Pari and Ventstream nebulizers (Fig. 9). The Pari LC Plus has a one-way valve in the top of the nebulizer that routes inspiratory flow through the chamber, "enhancing" the flow of the power-gas and aerosol delivery during inspiration. The Ventstream has the same nebulization chamber as the Sidestream, but the T-piece adaptor that attaches to the nebulizer cup has a flexible membrane inlet valve that allows inspiratory flow through the nebulizer, with a similar one-way expiratory valve in the outlet of the T-piece.[6] Dennis compared breath-enhanced, constant-output and ultrasonic nebulizers and concluded that breath-enhanced nebulizers "may promise better performance than either constant-output jet or ultrasonic nebulizers."[31] Knoch et al found in 2 studies that output with the Pari IS2, the Pari LC Plus, and the Pari Baby increased as a function of inspiratory flow.[41,42] Similar results were found by Coates et al, who compared tobramycin delivery from an open vent nebulizer (Pari LC

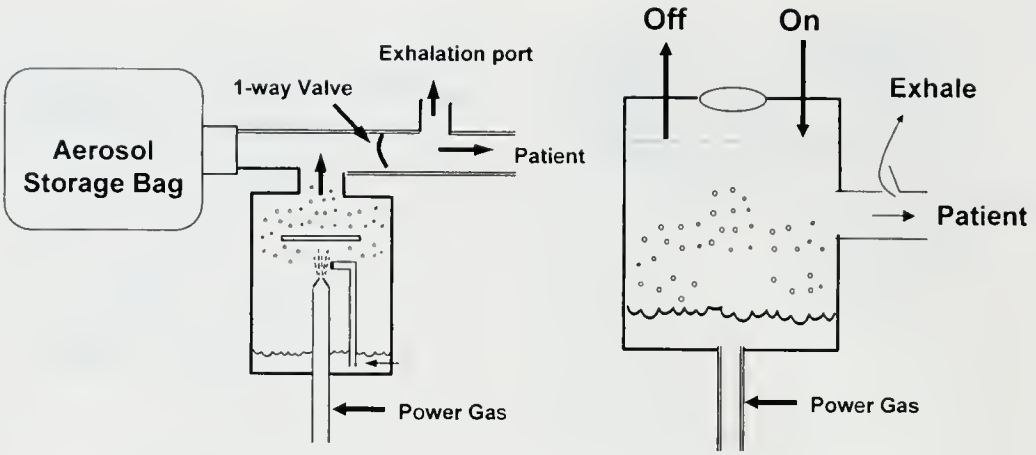

Fig. 10. Two examples of dosimetric nebulizers. Left: Circulaire. Right: AeroEclipse.

Jet Plus) and an unvented nebulizer (Hudson 1730).[43] This results from the design feature referred to as "breath-enhanced": the inspiratory flow is routed through the nebulizer by means of a one-way valve or simply an open vent, resulting in more aerosol delivery during inhalation than during exhalation. Larger tidal volume or longer inspiratory time would be expected to have the same effect. Measurements of total inhaled dose with the Pari LC and Pari LC Plus have ranged from a high of 25%[31] to a low of 19%.[23] However, Newman et al used radiolabeling and found that the total inhaled dose of 27% with the Pari LC (operated continuously, as with most clinical uses) partitioned into 12.8% lung dose and 14.2% to the mouth and stomach.[33] Using in vitro simulations, Dennis found that the Ventstream delivered a total inhaled dose of 24%, whereas Barry and O'Callaghan measured only 9.6%.[24,31] Dennis employed a sodium fluoride tracer, whereas Barry and O'Callaghan used a budesonide suspension, which may account for the observed difference in inhaled dose. In a nebulized suspension the solid drug particles leave the nebulizer through the medium of the droplets; if a solid drug particle is larger than the droplet, it will be trapped in the nebulizer.[44]

Dosimetric Designs. The Circulaire and the AeroEclipse nebulizers (Fig. 10) represent 2 approaches to inspiratory-only aerosol delivery. The same result can be achieved using a manual (thumb-operated) interrupter with a constant-output nebulizer, to alternate power-gas flow to the nebulizer or to the room. However, use of a manual interrupter with a constant-output nebulizer results in unacceptably long treatment times, since no nebulization occurs between inspirations, and the fill volume is usually $\geq$ 2.5 mL.

The Circulaire, which nebulizes continuously, contains the aerosol in a reservoir bag, and has a one-way valve between the bag and the mouthpiece, was designed in an attempt to convert a constant-output nebulizer to a dosimetric device. With correct use the valve design allows release of aerosol only during inhalation. However, if removed from the mouth with no inhalation, some aerosol may escape to the room through the one-way valve as pressure increases in the storage bag. In an in vitro study, Piper found that the Circulaire delivered a total inhaled dose of 0.32 $\pm$ 0.01 mg,[32] which was approximately 13% of the nominal dose of 2.5 mg albuterol. It should be noted that the emitted dose on inhalation was not measured directly, but calculated based on intermittent sampling. Mason et al used human volunteers and fill volumes of 3.5 mL of radiolabeled saline to compare the Circulaire's performance to a constant-output nebulizer, the Misty-Neb.[30] Subjects breathed normally, and the nebulizers were powered at 7 L/min by oxygen from a wall outlet. Lung deposition was 12.8 $\pm$ 5.1% with the Circulaire and 8.6 $\pm$ 1.6% with the Misty-Neb. The combined lung and stomach amounts compose the total inhaled dose, which was 13.9% with the Circulaire and 14.2% with the Misty-Neb. The dead volume was 37% with the Misty-Neb and 38% with the Circulaire. It is not clear why the dead volume is less in the Mason et al study of the Misty-Neb than in Lewis and Fleming's study of a similar conventional nebulizer.[29] The dead volume is also surprisingly low for the Circulaire, which would be expected to have large aerosol loss in the reservoir bag. This might be accounted for if only the nebulizer cup and not the entire reservoir bag and connecting piece were measured.

The AeroEclipse is a dosimetric nebulizer; it generates aerosol only during inspiration and is a "breath-actuated" device. An inspiratory flow of approximately 6 L/min activates the one-way valve in the top of the chamber and begins nebulization. Manual activation is also possible. Expired aerosol is routed through a one-way valve on the mouthpiece. The AeroEclipse is designed to allow nebulization with much smaller fill volumes than are com-

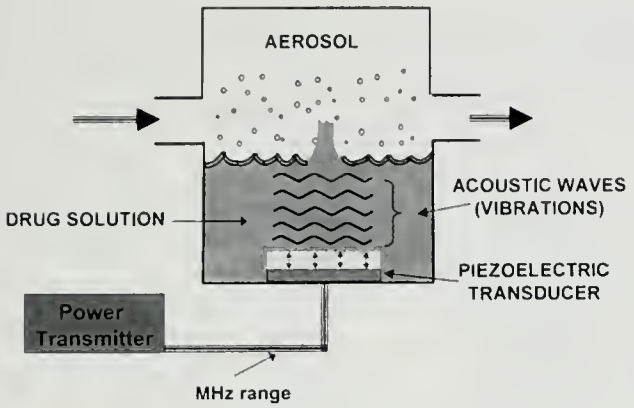

Fig. 11. Basic design and function of an ultrasonic nebulizer, which uses a piezoelectric effect to produce acoustic energy to nebulize the solution.

monly used; the manufacturer claims that a minimum volume of 1 mL can be used. Smaller volumes offset the longer treatment time otherwise caused by nebulization during inspiration only. An in vitro comparison by Hess et al showed that the inhaled mass in the fine particle fraction (< 4.7 μm) range was approximately 20% of a nominal 2.5 mg dose of albuterol with the AeroEclipse, compared to 15% with the Pari LCD.[45] The inhaled mass < 4.7 μm was only about 5% for the Circulaire in that study.

We recently compared the AeroEclipse with the Pari LCD and the Circulaire, using a breathing simulator and albuterol solution, and found that the AeroEclipse delivered a total inhaled mass of 39 ± 1.34%, compared to 15 ± 4.2% with the Pari LCD and 8.7 ± 0.99% with the Circulaire (unpublished data). The estimated lung dose, based on amount removed by a United States Pharmacopeia cascade impactor throat, was 34% with the AeroEclipse, 13% with the Pari LCD, and 7% with the Circulaire. The exhaled dose was approximately 18% with the Pari LCD, 12% with the Circulaire, and 7% with the AeroEclipse. As expected, dosimetric devices have lower ambient loss, with the breath-actuated AeroEclipse having the least exhaled loss.

Ultrasonic Nebulizers

Description and Basic Function

An alternative to jet nebulization is the ultrasonic nebulizer, which aerosolizes liquids by means of high-frequency acoustic vibrations produced by a piezoelectric transducer (Fig. 11). Ultrasonic nebulizers operate at high frequencies, in the megahertz range (millions of cycles per second), and with power ranges below 30 watts/cm^2.[46] A distinction can be made between higher power humidifying nebulizers, referred to as "fogging machines" in older literature, and lower power drug nebulizers. The continuously operated ultrasonic nebulizers had a high output, used a continuous liquid feed, and were used to provide humidity in oxygen tents and at the bedside. Design features included either a flat or focused transducer and the presence or absence of a couplant liquid. A focused, curved transducer requires a precise solution level for aerosolization. A couplant can protect the transducer from the solution to be nebulized but may attenuate the acoustic energy of the vibrations produced by the transducer. Table 3 lists operating specifications from manufacturers and available data on particle size.

Physics of Ultrasonic Nebulization

Piezoelectric Effect. The piezoelectric effect is the ability of some materials to convert (transduce) mechanical energy to electrical energy, and vice-versa. It is a reversible, electromechanical interaction that occurs in certain quartz crystals and ceramics such as lead zirconate titanate or barium titanate.[51,52] The *direct* piezoelectric effect is the generation of an electric charge, or potential difference, across a crystal as a result of applying mechanical strain (expansion or contraction) to the crystal. The *reverse* or *converse* piezoelectric effect is the opposite: application of an electric charge causes the crystal to change its shape. Medical ultrasonic nebulizers use the converse effect. The polarity and magnitude of the charge determines the direction and magnitude of the deformation produced (Fig. 12). When an alternating electric field (alternating polarity, alternating current) is applied, the crystal expands and contracts at the same frequency as the electric field. The magnitude of the vibration depends on the magnitude of the applied electrical charge.[53] When the charge is removed, the strain stops, and, similarly, removing the mechanical strain ends the charge produced; hence the reversibility. Ceramics such as lead zirconate titanate have a higher piezoelectric coupling than quartz crystals; that is, there is a larger force resulting from a given electric signal.[52] The most common materials used in ultrasonic generators (in order of increasing theoretical efficiency) are quartz, barium titanate, cobalt barium titanate, and lead zirconate titanate.[46] The term "piezo" is from the Greek term "to squeeze," aptly describing the behavior of a piezoelectric crystal.[52] The direct effect was originally discovered by the Curie brothers, Jacques and Pierre, in 1880.[52] The converse effect was predicted the following year by Lippmann, and then verified by the Curie brothers.[51,52] Practical applications of the effect did not appear until the 20th century. One of the most common applications is the battery-operated "quartz watch," which uses a quartz piezoelectric resonator to regulate the electronic clock mechanism.[51] This is one example of many frequency control and timing applications of quartz crystal devices. Other

Table 3. Selected Operating Specifications or Data for Some Ultrasonic Nebulizers

Nebulizer	Transducer Frequency (MHz)	Output Rate (mL/min)	MMAD (μm)	CMD (μm)	Source or Reference
DeVilbiss PulmoSonic	2.4	0.5	< 3.5	—	Manufacturer
DeVilbiss AeroSonic	2.25	0.35	1.8	—	Manufacturer
" "	—	—	4.54	—	31
OMRON NE-U03V	65 kHz	0.25	range: 1–7	—	Manufacturer
Bennett US-1	1.35	≤ 3	—	—	Manufacturer
DeVilbiss 880 (1 and 2)*	1.35	—	5.7	3.5	47
DeVilbiss 880 (3 and 4)*	1.35	—	6.9	3.5	47
Mist-O_2-Gen EN140	1.4	—	6.5	3.9–4.0	47
Monaghan 650 (5)*	1.65	—	5.1	—	14
Monaghan 650 (10)*	1.65	—	5.2	—	14
DeVilbiss 65	1.35	—	6.3–7.1	0.22–0.33	48
Monaghan 670	1.65	—	5.2–5.7	0.39–0.41	48
Omron NE-U10	1.7	—	6.2	0.27	48
DeVilbiss Pulmosonic	1.25	—	6.4–6.8	0.33	48
" "	—	—	5.4 (0.1)	—	49
Microstat	1.8	—	4.02	—	31, 50

MMAD = mass median aerodynamic diameter
CMD = count median diameter
*Power setting on nebulizer

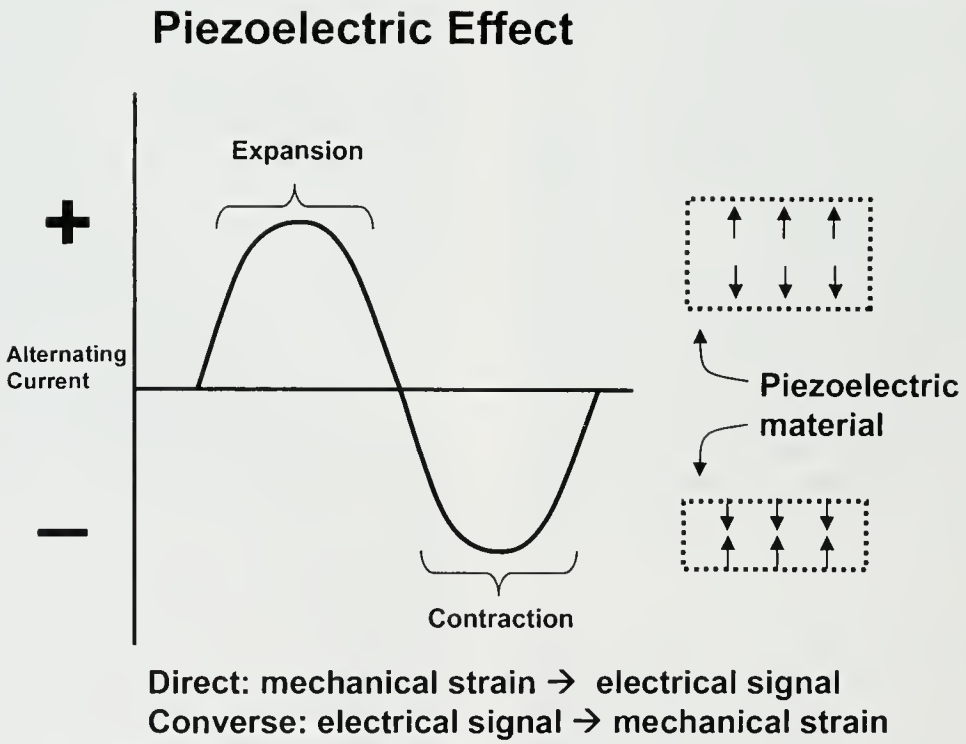

Fig. 12. The relationship between an electric current and the change of shape (expansion and contraction) of a piezoelectric material such as quartz or lead zirconate titanate.

uses of the piezoelectric effect include ultrasonic cleaners, lighters, and gas grill ignitions. The latter 2 items use the direct piezoelectric effect. The use of the piezoelectric effect in medical ultrasonic nebulizers was introduced in the 1960s. The term "ultrasonic" generally refers to frequencies above 20,000 Hz (20 kHz).[5] The range of frequencies for medical nebulizers is in the millions of hertz, or megahertz (MHz), range, and hence the term ultrasonic.

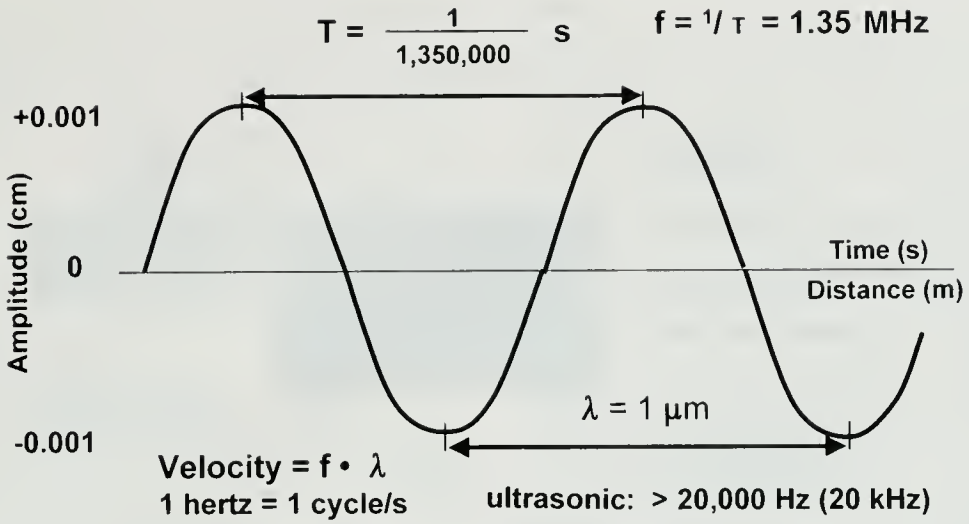

Fig. 13. Quantities used to describe a periodic wave, assuming simple harmonic motion.

Wave Characteristics. The electrically induced expansion-contraction vibration of a piezoelectric crystal produces acoustic waves. A wave is defined as a periodic disturbance. Assuming that only simple harmonic motion is involved, there are 5 quantities given in standard physics texts[5] to describe a periodic wave:

- Period (T): the time for 1 complete vibration
- Frequency (f): the number of vibrations per unit time
- Amplitude (A): the maximum displacement of any particle measured from its equilibrium position
- Wavelength (λ): the distance between any 2 successive points that have the same phase
- Wave velocity (v): velocity (distance/time) with which any specific point is propagated

These quantities are illustrated in Figure 13, for a waveform with a period of 1/1,350,000 s, a corresponding frequency of 1,350,000 cycles per second (1.35 MHz), and a wavelength of 1 μm. An amplitude of approximately 0.001 cm is shown. The relationship between wavelength, frequency, and velocity is:

$$\text{Wavelength} = \text{Velocity/Frequency}$$

or

$$\lambda = v/f$$

Therefore, velocity for the latter wave would be calculated with the equation:

$$v = \lambda \times f$$

Filling in the values, we have

$$v = 1\ \mu\text{m} \times 1{,}350{,}000\ \text{cycles/s}$$

$$v = 1{,}350{,}000\ \mu\text{m/s}\ (1.35\ \text{m/s})$$

The quantities of frequency, wavelength, and amplitude, along with the concept of power (in watts or watts/cm^2) for the electric signal, will all be used in analyzing aerosol production by ultrasonic nebulizers.

Theory of Aerosol Production

The exact mechanism of aerosol production with ultrasonic nebulizers is surprisingly uncertain. Originally, ultrasonic aerosol production using the piezoelectric effect was explained based on capillary wave formation (the "capillary wave theory"), in which droplet size is a function of frequency: higher frequencies produce smaller droplets. The work of Lang, published in 1962, established this theory as the mechanism of ultrasonic aerosol generation.[54] Lang's equations were developed mostly with thin liquid films, using frequencies in the range of 10 to 800 kHz, which is lower than the frequencies of medical ultrasonic nebulizers. In 1973, Topp found that the capillary wave mechanism does not explain well the broader size distributions with larger liquid films, nor does it explain the lack of correspondence between droplet size and frequency in the megahertz range of ultrasonic nebulizers.[55] Cavitation phenomena had been proposed even before Lang's work, to explain the variation in aerosol size, and subsequently the 2 theories were related, to state that aerosol formation takes place from capillary waves driven by cavitation bubbles.[55] However, in ultrasonic nebulizers a fountain is created that emits fine mist. The process of fountain formation and disintegration occurs with sufficient intensity at high frequencies (above 0.5 MHz), with fine droplet formation that is essentially independent of the frequency.[46] These mechanisms are described below. Traditionally cited reviews of the mechanism of ultrasonic nebulization give only the equations derived by Lang for the capillary wave theory.[6,56,57]

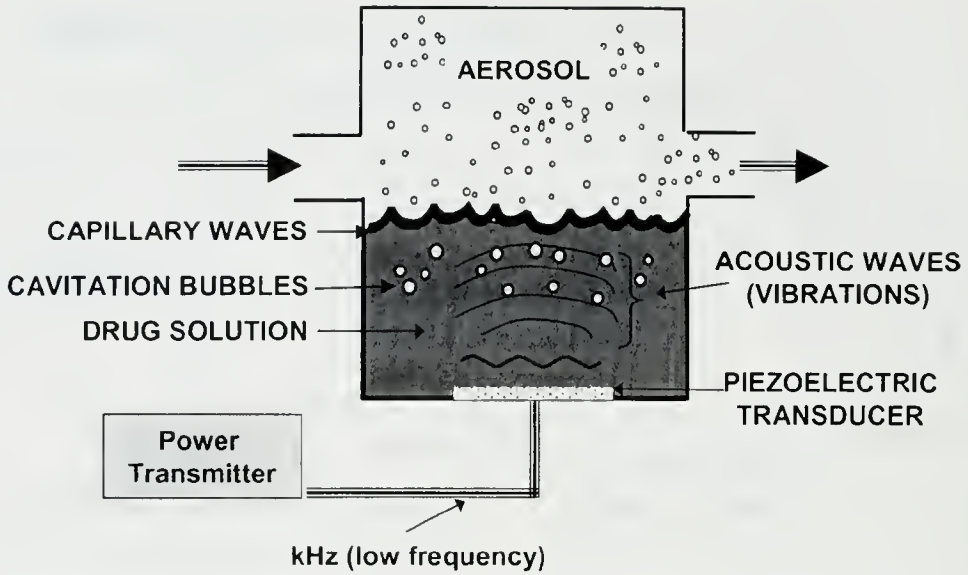

Fig. 14. A possible explanation for aerosol formation by an ultrasonic nebulizer. Aerosol is produced by droplets formed from instability of capillary wave crests. Cavitation bubbles are formed by alternating compression and expansion of solution and drive the formation of capillary waves.

Capillary Wave Theory. The capillary wave theory states that aerosol formation begins when a certain threshold wave amplitude in the solution is induced by the vibrations of the piezoelectric transducer. At that threshold, small waves, termed "capillary waves," are produced on the surface of the solution. The threshold amplitude is calculated as:

$$A_t = 4\nu/f\lambda_k \quad (1)$$

in which ν is kinematic viscosity of the solution, f is frequency of acoustic waves from the transducer, and λ_k is capillary wavelength. As the acoustic frequency increases, the threshold for aerosol generation decreases. The threshold also increases with increasing solution viscosity. Once this threshold is exceeded by a factor of approximately 4, capillary waves grow until instability at the wave crests produces droplets.[50,57] Figure 14 illustrates the capillary wave theory of aerosol production and cavitation effects. Capillary wavelength is a function of the frequency produced by the piezoelectric transducer, and is calculated as:

$$\lambda_k = (8\pi\gamma/\rho f^2)^{1/3} \quad (2)$$

in which γ is the surface tension of the solution, ρ is the density of solution, and f is the acoustic frequency produced by the piezoelectric transducer. The capillary wavelength is inversely related to frequency and density, and it is directly proportional to surface tension. Lang found that the count median diameter (CMD) of aerosol droplets produced is correlated to the wavelength by a factor of 0.34:[54,56,57]

$$CMD = 0.34\ \lambda_k \quad (3)$$

Therefore the count median diameter of droplets is smaller with smaller wavelengths, and smaller wavelengths occur at higher frequencies (Equation 2). A factor of 0.36 was subsequently derived for the proportionality constant, for drop formation by high-amplitude capillary waves.[55]

Cavitation Effects. Ultrasonic cleaners use high power with low-frequency ultrasonic waves to produce a scrubbing cavitation. During the half-cycle when the transducer moves toward the solution, there is compression (high pressure). When it moves away from the solution in the second half of the cycle, there is rarefaction (low pressure). With sufficient power (amplitude), the pressure on the liquid can be below the liquid's vapor pressure and minute bubbles are formed.[52] The formation and subsequent implosion of vapor bubbles is called cavitation. The *cavitation theory* postulates that implosions of the bubbles close to the liquid surface generate enough disturbance to produce aerosol droplets. This is also shown in Figure 14.

The merger of the capillary wave theory with the cavitation theory led to the proposal that droplet formation occurs from capillary waves initiated and driven by cavitation bubbles.[55,56]

Fountain Formation and Disintegration. There have been several criticisms of the capillary wave and cavita-

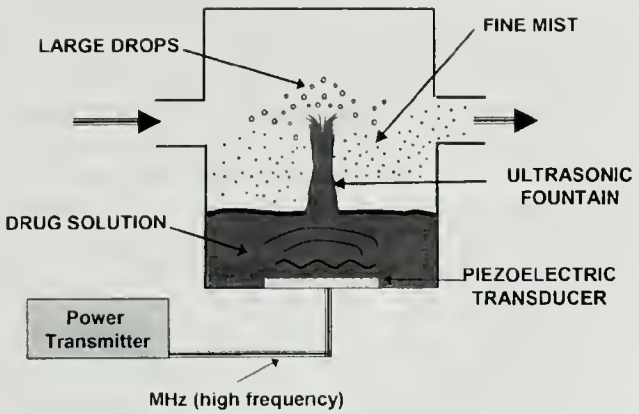

Fig. 15. Fountain formation occurs at the frequencies (> 0.8 MHz) and power levels used in ultrasonic nebulizers. An ultrasonic fountain is produced by radiation pressure, which results in a fine mist emitted from the fountain. Large drops produced at the top of the fountain fall back into the solution.

tion explanation of ultrasonic aerosol production. It is claimed that the relationship between droplet size and acoustic frequency applies from about 10 kHz into the megahertz range.[57] However, Boucher and Kreuter pointed out that the relationship between droplet size and frequency holds at low frequencies, below about 0.5 MHz (500 kHz), but not at higher frequencies of ≥ 0.8 MHz (800 kHz).[46] As the frequency increases, the power required to produce cavitation increases. At 800 kHz (0.8 MHz) the frequency for water is below the cavitation threshold, assuming a power of about 10 watts/cm^2. Most medical ultrasonic nebulizers use < 50 watts/cm^2 and most use 10–30 watts/cm^2. At the frequency and power range used in ultrasonic nebulization a different mechanism of fountain formation occurs. As shown in Figure 15, at this higher frequency there are no cavitation bubbles. A strong upward force aligned on the transducer's main axis pushes a column of liquid into the air. This force is due to radiation pressure, not acoustic pressure, and is calculated by:

$$P_r = W(1 + \gamma)\ \text{dyn/cm}^2 \qquad (4)$$

where W is the energy density in ergs/cm^3, and γ is the ratio of specific heats of the irradiated medium.[46] This pressure causes the fountain characteristic of medical nebulizers. In the range of 0.5 to 4 mHz, the nebulization is essentially independent of the frequency and there seems to be no cavitation.[46] Aerosol formation occurs with an increase in the ultrasonic intensity above some critical value. At medium power (< 30 watts/cm^2) the aerosol formation occurs in the lower part of the fountain. Fine droplets are released in bursts in that region, at regular intervals of a few hundred per second. At a much higher power (> 30–50 watts/cm^2) there is continuous aerosol formation along the height of the fountain. Boucher and Kreuter found that at frequencies higher than about 0.5 MHz, fountain disintegration becomes the predominant factor, and no theoretical or experimental formula relating droplet size to frequency has been established for this mechanism.[46] At identical power output there is no reason to expect large variation in size distribution of droplets produced at frequencies > 0.5 MHz.[46] The capillary wave mechanism and corresponding relationship of droplet size to solution wavelength and frequency also do not explain the fact that the size distribution of aerosols becomes broader with larger solutions (thicker films).[55] In support of this, Boucher and Kreuter refer to data published by Mercer et al on aerosol size with 3 ultrasonic nebulizers (Table 4).[46,47]

The MMAD is calculated using Lang's equation for the capillary wave theory, which states that particle count median diameter decreases with higher frequencies.[47,54] But increasing frequencies of the 3 nebulizers does not result in a trend of decreasing particle size. Boucher and Kreuter noted that the air stream pattern with ultrasonic nebulization may influence particle size,[46] but Sterk et al evaluated 9 different ultrasonic nebulizers and found that the volume median aerodynamic diameter was inversely related to the ultrasonic frequency, with an r value of −0.66.[48] This may imply that droplet size is influenced by frequency, as stated by the capillary wave theory, but that other factors are involved, including baffling of particles by internal geometry and air flow effects.

Comparison of Ultrasonic and Jet Nebulizers

There are several differences in operating features between jet and ultrasonic nebulizers (Table 5). Small-volume jet nebulizers generally have a lower rate of output than ultrasonic nebulizers, but particles produced by jet nebulizers tend to be smaller. Sterk et al found that solution output from ultrasonic devices was 2–10 times greater than that from jet nebulizers. The droplet size generated by jet nebulizers was 1.5–4 μm, whereas with ultrasonic nebu-

Table 4. Operating Frequencies, Calculated Mass Median Diameter, and Measured Mass Median Diameter for 3 Ultrasonic Nebulizers

	Frequency (MHz)	Calculated MMAD (μm)	Measured MMAD (μm)*
Mist-O_2-Gen EN 140	1.4	3.7	3.9
DeVilbiss 880	1.35	3.8	3.5
Ultramist III	0.8	4.9	3.9

MMAD = mass median aerodynamic diameter
*Based on cascade impaction
(Adapted from Reference 47)

Table 5. Comparison of General Operating Features and Effects of Jet and Ultrasonic Nebulizers

	Jet	Ultrasonic
Output rate	Lower	Higher
Particle size	Smaller	Larger
Temperature (solution)	Cools	Heats
Solution concentration	Increases	No change
Dead volume	Smaller?*	Larger?*

*Little data available
(Adapted from Reference 49.)

lizers the diameter range was 3–7 μm.[48] The output of the ultrasonic nebulizer is a function of the power setting, which regulates the amplitude of the acoustic waves produced. Boucher and Kreuter measured the aerosolization rate with the DeVilbiss 880, which offers variable power settings. The power setting 1 on the DeVilbiss 880 represented 35 watts and produced an output rate of 51 mL/h.[46] At the highest power setting (4, equivalent to 120 watts), the output rate was 340 mL/h. Ultrasonic nebulizers for drug inhalation, such as the AeroSonic or PulmoSonic, do not usually allow variation of the power setting.

Temperature change during nebulization also differs between jet and ultrasonic nebulizers. The acoustic energy imparted to the solution in an ultrasonic nebulizer causes aerosol production, but much of the energy dissipates as heat.[47,50] Phipps and Gonda found that nebulizer solution temperature with a Mist-O_2-Gen EN 143A increased over 30 min from about 23° C to over 40° C.[12] Niven et al also found that solution in an AeroSonic increased from 20° C to over 50° C.[50] In addition, that study found a sizable differential between the temperature in the fountain, which was hotter, and the surrounding solution. Fink and Uster reported a 24° C increase with the Siemens 345 ultrasonic nebulizer.[58] A deviation from this general trend with ultrasonic nebulizers was seen in a study by Dennis et al, using the Microinhaler ultrasonic nebulizer, in which solution temperature rose only 1 degree after 6 minutes.[15] The amount of power and the duration of the acoustic vibration probably influence heat production in the solution.

Niven et al found that the increase in solution temperature is associated with an increase in aerosol output from an ultrasonic nebulizer. Solute output increased more than 5-fold as solution temperature increased from approximately 21° C to 50° C, using lactate dehydrogenase.[50] The increased output was not due to concentration increases, since only a 5.5% increase in concentration occurred over the 10 minutes of testing. An alternative explanation is that the increase in temperature decreases solution viscosity. In the capillary wave theory the threshold for capillary wave formation and aerosol production is directly proportional to viscosity. However, Niven et al pointed out that the change in viscosity of water between 20° and 50° C is small, on the order of 0.5 centipoises.[50]

A third difference between jet and ultrasonic nebulizers is the effect of the nebulization process on solution concentration. As early as 1976, in a study by Ferron et al evaluating both jet and ultrasonic nebulizers, it was observed that evaporation in a jet nebulizer cools the solution and increases the concentration of the remaining solution.[14] Ferron et al found no change in a concentration of salt solution nebulized by a Monaghan 650 ultrasonic nebulizer. Dennis et al also found that the Microinhaler ultrasonic nebulizer dissipated 4 out of an original 5 mL of solution with no change in the reservoir concentration of the fluoride solution.[15] Because of this lack of evaporation and concentration change, use of weight change (gravimetric method) to estimate aerosol output is relatively accurate with an ultrasonic nebulizer.[15]

There are few data available on drug mass in the dead volume with ultrasonic nebulizers. However, a study by Newman et al, using hypertonic (7%) saline containing 280 mg in 4 mL of solution, compared dead volume mass of the PulmoSonic and the DeVilbiss 646 jet nebulizer. The PulmoSonic left an average ± standard deviation of 1.32 ± 0.16 mg in the residual solution, whereas the jet nebulizer left 0.88 ± 0.06 mg at 6 L/min and 0.56 ± 0.03 mg at 12 L/min.[49]

Advantages and Disadvantages of Ultrasonic Nebulizers

Table 6 summarizes the advantages and disadvantages of ultrasonic nebulization. Ultrasonic nebulizers require

Table 6. Advantages and Disadvantages of Ultrasonic Nebulizers

Advantages
- Patient coordination not required
- Portable
- Dose modification and high doses possible
- Rapid nebulization and small solution amounts compared to jet nebulizers
- No aerosol loss during exhalation
- No use of propellants, such as CFCs or HFAs
- Small residual drug (dead) volume
- Quiet operation

Disadvantages
- Expensive
- Lack of durability
- Need for external power source (alternating or direct current)
- Length of time for set-up, treatment, cleaning
- Possible contamination with inadequate cleaning
- Possible drug degradation
- Inability to nebulize suspensions well
- Increased viscosity and surface tension limit ability to nebulize
- Possible airway irritation with bland solutions
- Electrolyte imbalance in infants with continuous inhalation

only a normal breathing pattern and offer faster nebulization and thus shorter treatment times. Nevertheless, jet nebulization remains the more common method in the United States and probably throughout the world, perhaps because of the higher cost and lower durability of ultrasonic nebulizers.

Another concern about ultrasonic nebulization is over the effects of intense ultrasonic vibration on drug stability. Two effects with ultrasonic nebulization could affect drug stability. The heat produced with sufficient power and time could degrade thermolabile proteins. It has been reported that insulin was inactivated by ultrasonic nebulization.[59] Dornase alfa (rhDNase) can be aggregated by ultrasonic nebulization if the melting temperature of the protein is exceeded.[50] A test protein, the enzyme lactate dehydrogenase (LDH), was completely inactivated after 20 min of operation of an AeroSonic nebulizer.[50] The other effect is the theoretical potential to break covalent bonding within a chemical structure, by the sizable g forces generated with ultrasonic vibration. Boucher and Kreuter calculated that a frequency of 800 kHz (0.8 MHz) at 10 watts/cm^2 could produce a maximum acceleration of 183,000 g in the solution.[46] Acceleration values $>$ 500,000 g could easily break single, double, and triple bonds.[46]

The physicochemical properties of the drug solution may also affect an ultrasonic nebulizer's ability to create a suitable aerosol. The threshold amplitude for nebulization to occur, as shown in Equation 1, is directly proportional to solution viscosity. Higher viscosity raises the threshold for aerosol formation. Boucher and Kreuter examined aerosolization of Alevaire (a compound of tyloxapol, bicarbonate, and glycerin, which is no longer available) and Mucomyst (N-acetylcysteine), and reported that higher-viscosity solutions are difficult to nebulize. They stated that the threshold viscosity was about 10 centipoises, and above that level aerosol output declined.[46] McCallion et al found that droplet size was proportional to viscosity (not just acoustic frequency) and that more viscous solutions had longer nebulization times, with lower total and respirable outputs.[60] No nebulization occurred above certain viscosities.

There is evidence that with an ultrasonic nebulizer drug *suspensions* do not nebulize as well as *solutions*. In a solution, drug particles are dissolved into a homogeneous, single, liquid phase, whereas a suspension is a dispersion of particles in a liquid. Both jet and ultrasonic nebulizers show significant differences in output between solutions and suspensions.[61] Nikander reported that a conventional jet nebulizer (Spira E4) and a dosimetric ultrasonic nebulizer (Spira Ultra) gave an inhaled mass of 47% and 48%, respectively, with terbutaline solution, but only 32% and 9.8%, respectively, with budesonide suspension (Fig. 16).

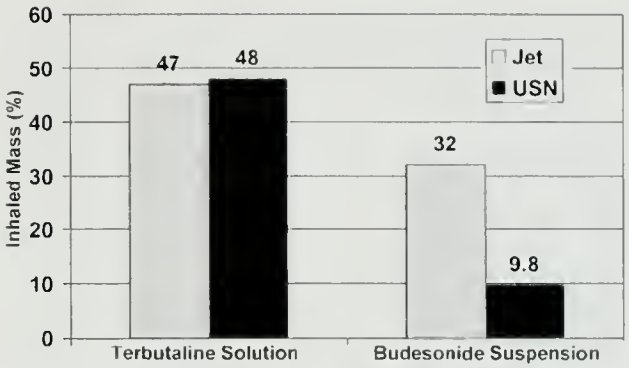

Fig. 16. Ability of a jet nebulizer (Spira E4) and an ultrasonic nebulizer (Spira Ultra) to aerosolize a solution of terbutaline versus a suspension of budesonide. (Based on data from Reference 61.)

Similarly, the Pulmosonic gave a much higher output with a solution of sodium chloride than with a suspension of budesonide.[44] For a jet nebulizer, if a solid drug particle is larger than the droplet produced, the particle is trapped in the nebulizer,[44] which limits total output. With ultrasonic nebulizers it is theorized that suspended particles settle and thus tend not to reach the surface where nebulization occurs.[44,62]

The larger aerosol output seen with ultrasonic nebulizers contributes to some of the hazards listed in Table 6. Airway irritation and changes in pulmonary mechanics and blood gases have been reported with inhalation of bland solutions.[63,64] This was particularly noted in patients with chronic obstructive pulmonary disease, who experienced a 5–22 mm Hg decline in P_{aO_2}.[65] There was also a case report of a 3-day-old baby boy who developed edema, polyuria, and hyponatremia while on ventilatory support using an ultrasonic nebulizer for humidity.[66]

Summary

In the closing of the 20th century the role of nebulizers in delivering aerosolized drugs began to broaden beyond the topical treatment of pulmonary diseases. The large surface area provided by the airways for the systemic absorption of drugs is leading to the aerosolization of drugs such as insulin and morphine. The ability to aerosolize various solutions makes nebulizers attractive and feasible for aerosol treatment of both pulmonary and nonpulmonary diseases and problems. But such uses demand greater efficiency and precision from nebulizers, some of which are discussed in the other conference reports in this and the following issue of Respiratory Care.

Considering the designs, advantages, and disadvantages of current jet and ultrasonic nebulizers, it is obvious that neither type provides the ideal medical inhaler device.

Table 7. Criteria for an Ideal Medical Inhaler in Relation to Jet and Ultrasonic Nebulizer Function and Features

Ideal Inhaler	Jet	Ultrasonic
Dose reliability, reproducibility, accuracy	No	Yes
Small particle size of 1–5 μm	Yes	Yes
Simple to use and handle	Yes/No*	Yes/No*
Small size, easy to carry	No	No
Multiple dose capability	No	No
Resistance to bacterial contamination	No	No
Durability	Yes	No
Cost effectiveness	Yes	No
Minimal or no dead volume	No	No
No ambient aerosol contamination	No	No

*Yes: patient breathing coordination not required. No: assembly and cleaning can be confusing.
(Adapted from Reference 67.)

Table 7 compares Wolff and Niven's criteria for a perfect aerosol device with the features of current jet and ultrasonic nebulizers.[67] Newer aerosol device designs will need to administer drugs quickly and efficiently, with dose-reproducibility and without the need of complex breathing maneuvers, in an easy-to-use device that is durable and cost-effective and that causes no ambient contamination by lost aerosol.

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Discussion

Hess: Joe, from a clinical perspective, can you give me any suggestions as to when I would want to use an ultrasonic nebulizer rather than a jet nebulizer?

Ran: You know, I have to be candid and say I really don't have a good reason to, myself. They are certainly convenient, and it's claimed that they can aerosolize at a much faster rate. That may be; however, Dr Dennis's data don't support that. Truthfully, I think if you take all the factors into consideration, such as cost and durability, I think the jet nebulizer dominates the market, and that's *why* it dominates the market. I don't know of a good reason to use an ultrasonic nebulizer.

Dennis: I want to compliment you on summarizing a broad area. However, I think it's maybe a bit dangerous to generalize about jet versus ultrasonic nebulizers, because within each category there is so much variation. We tend to generalize on the basis of what we see in the literature. We find some useful references and we draw our conclusions from what's published or what we find, but that's often not very comprehensive, so there's a lot more information out there.

It's difficult to generalize and make conclusions based on what we see in

the literature and the literature people reference when there could be a lot more information out there, or a lot of work that hasn't been done, or that's been done and not seen the light of day. To generalize about performance differences between devices can be divisive, but it has to be done, because how else can we deal with the subject?

Rau: I did really find a trend [see Table 2 and Figures 3, 4, and 5], but I agree with you that differences in the testing conditions can make quite a difference. I think in your study you used 3 mL with the ultrasonic nebulizers. I'm not quite sure how low you can go in filling volume with them. There may be a little more versatility with an ultrasonic nebulizer regarding the volume to be nebulized than there is with a jet nebulizer. I know when we studied the Microstat nebulizer in the hospital, the major claim was that you can put a very small amount of albuterol in there and decrease the nebulization time. So I think your point is well made, and certainly the conditions of testing have a lot to do with it.

Dennis: I'll note a point about test conditions, which relates to some work I did. I was doing contract work on behalf of a manufacturer (and acknowledged that in the report) but *they* selected the volume fill for testing. If the fill had been different, say 2 mL or 1.5 mL, I wouldn't say the order of results would be different, but you can certainly make the results look very preferable by the choice of fill volume—forget other methods of testing. That's within the same paper, within the same technique, and if you look at the differences between papers it's very difficult to generalize and judge what's real. What we should depend on is useful information.

Smaldone: I enjoyed your presentation. I thought it was a very difficult subject, and I agree with the comments regarding generalization. Regarding the issue of the waves and the lack thereof versus the fountain in an ultrasonic nebulizer, from an engineering point of view, those observations reminded me of the old physics experiments on wave propagation and summation. Possibly the waves *are* there and the fountain is really a coincidence summation effect from the waves and possibly the size of the chamber, and therefore the wavelength is important. That is, the waves probably reflect off the side of the chamber and add up to make the fountain. In those old physics experiments you would have probes bouncing in a pool, and you'd watch waves come off, and then as they interact with the walls of the pool and cause reflection you can get either additive effects or canceling effects. It could be that the chamber size is critical in terms of designing the aerosol output of ultrasonic nebulizers.

Rau: That's a good point, and it reminded me of something I failed to mention. Certainly it's been theorized that part of the effect on the particle size is the gas flow through the chamber, whether it's an inspiratory flow or a constant gas flow in the nebulizer, as well as the internal geometry that creates some baffling within the nebulizer, but recent reviews suggest you're absolutely right. I think the problem is that we have not seen a really lucid explanation of how atomization occurs in medical ultrasonic nebulizers, taking into account the frequencies and amount of power used. Recent reviews all cite the sort of standard dogma of the capillary wave theory that Robert Lang described.[1–3]

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Smaldone: Right. The mechanism could still be wave related, and the reason you see a fountain and don't see waves is that the waves are all adding up into a fountain. Regarding the particles, the conditions after the particles are created are probably just as important in an ultrasonic nebulizer as they are in a jet nebulizer. The primary particles often have very little to do with what you get for secondary particles.

Tom O'Riordan and I did a study with the FisoNeb[1] that involved actual clinical aerosol delivery measured with that device, and the FisoNeb (which lost out in the pentamidine era, probably due to marketing and political issues) was a very effective device. It delivered aerosol much more rapidly than the Respirgard nebulizer, and it was an effective delivery system. Bench studies that we did on that device[2] suggested that its characteristics were largely due to internal baffling, which enabled it to take larger droplets and make a small-droplet, respirable aerosol; and the treatment time was quite short. So, again, there may be general points that can be made, but the specific issues can be important.

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Barry: Thanks for an excellent presentation. One aspect that you didn't cover about jet nebulizers was the compressor. One of my interests is in high-altitude medicine, and when we tried to nebulize at an altitude of 5,000 meters the jet nebulizers didn't work, because the compressors didn't work. I think people often forget that the compressor is an integral part of the jet nebulizer and must be considered with it, and that one aspect of nebu-

lizers is whether you can use them at altitude with constant output. You also see reduced nebulizer output at about 2,000 feet; in Colorado, for instance, it's an issue. So if you're using a compressor, that has to be considered as part of the nebulizer system.

Rau: Absolutely!

Fink:* I am familiar with John Dennis's concept of continuous breath-enhanced and breath-actuated nebulizers, but I was surprised that you described the Circulaire as a dosimetric device, because it looks more like the Piper device than the AeroEclipse. Clearly, from your data the Circulaire was much less efficient than breath-enhanced or breath-actuated nebulizers. I tend to think of dosimetric nebulizers as those used in pulmonary function labs, which are breath-actuated. Why did you extend the definition to include the Circulaire?

Rau: I am not sure that we would agree that dosimetric implies only breath-actuated. Maybe we can reach consensus at this meeting, which would be helpful to all of us, I think. I based it on the delivery of aerosol only during inspiration.

Inspiratory-only delivery can be achieved in 3 ways that I know of. One is with the breath-actuated AeroEclipse, which is probably the most sophisticated device at the moment. Second is to use a simple thumb interrupter, which is something we used to do years ago; the Pari LL uses that technology. The third is the system used by the Circulaire, because of its valving mechanism.

That method may be the crudest of the 3. I don't think it works very well, to be blunt; my measurements indicated that it only delivers about 6 or 7% of the inhaled mass, although that conflicts with some of the available data. The data from Mason [see Table 2] did not even add up to 100%.[1] Where was the other 40% that was never acknowledged? Presumably it was in the Circulaire's bag. But the reported 12% that was delivered to the lung was pretty optimistic. Piper's study[2] and my study (unpublished data) found that about 6–7% in vitro would reach the lung.

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Fink: Well, I would propose that perhaps it's more appropriate to consider the Circulaire as a continuous nebulizer with reservoir system, rather than a breath-actuated or dosimetric device.

Rau: I think, then, that the issue becomes how you define dosimetric?

Fink: That's right.

Rau: I was generous in that definition and therefore included the Circulaire with the dosimetrics.

Fink: I understand, but I am concerned that that broad definition might generate some confusion as the clinical community attempts to understand the impact of the operating principles of these nebulizers.

Dunne: Regarding the single-patient-use, disposable jet nebulizer; have you researched the performance decay of those devices over time? They are so mass-produced and relatively inexpensive.

Rau: No, and that's a good question. I don't know if anyone has any data on their life span or shelf life or how long a patient should use them at home. In the hospital it's not that much of an issue, because they use it for several days and then change it out. But at home it is an issue. When do you tell a patient to replace that nebulizer?

Smaldone: That's a very good question. You have to thank AstraZeneca for some of this work, because in bringing budesonide to the market they did test the delivery systems over time. For example, the Pari device has been tested maybe 60 times in a row (the same device), and that is not part of the testing required under section 510(k) [of the Food, Drug, and Cosmetics Act]. That study[1] was driven by the supporting pharmaceutical company for the specific drug. It's an important regulatory issue that has not been formally addressed by the Food and Drug Administration. The fact that most devices are approved for single-use-only gets them off the hook. Yet, in reality most nebulizers are expected to be used repeatedly. If there's going to be a drug involved with the device, then more attention might be paid to those issues, but right now I don't think it's a requirement, so it's up to the user to decide what to do.

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Dolovich: There has been work done on reproducibility of different units of the same type for repeated use by patients. One of the concerns at the time was that some of the jet nebulizers had a baffle insert that was removed for cleaning. The baffle slipped over the top of the capillary tube that draws up the liquid, and if the baffle was not positioned correctly, aerosol delivery was affected. So you just need to go back into some of the earlier literature and have a look at those papers. It still may be an issue.

My other comment is that one should consider other uses for these

devices, ultrasonic or jet, and I mention this because if you're doing sputum induction, for example, you don't want to use a small-particle, low-output jet nebulizer. You want a large-particle, high-volume nebulizer to enable the saline to target the central airways. So that means an ultrasonic nebulizer such as the FisoNeb, which, unfortunately, burns out after 7–10 minutes. We use a bank of nebulizers and keep changing them in order to get our samples. So there are lots of clinical issues to consider when using nebulizers.

I wonder, Joe, whether you could give us a sense of the number of new devices, jet or ultrasonic, that are put on the market every year. In other words, new variations on the same theme. Are manufacturers coming out with new types of nebulizers that aren't really detailed in the literature?

Rau: I don't know what the data on that is. It's almost a marketing question, and I admit I'm not sure. My clinical sense is that it's not a *huge* number. We've got this cadre of disposable jet nebulizers that dominates most of our aerosol device use, but I don't know the answer to that.

Barry: In a jet nebulizer does the baffle only filter out large particles or does it have a role in generating small particles?

Rau: I think the latter—the former *and* the latter, to some extent. The ultimate aerosol particle emitted, as I understand it, is a function of that baffling system. In the process of that baffling there is a good degree of rain out and coalescence that drains back into the reservoir, until ultimately enough aerosol gets out and it begins to sputter. But that baffling process certainly creates those smaller particles. The secondary droplets are much smaller than the primary droplets at the jet where the 2 fluids mix. That's my understanding of it.

Geller: Most literature from compressor manufacturers states that the device puts out a certain liter flow, and yet when you put a resistance on it, it changes the liter flow, depending on the resistance of the device. Sometimes the compressor puts out almost no flow when that happens. Can you comment about compressors and what the end users can expect from them.

Rau: That's a good question. I did not, as Peter Barry acknowledged, say much about the compressor-nebulizer combination, but the compressor is a key factor. That reflects my background, because I primarily use wall flow meters with 50 psi, so we're able to get 6, 8, or 10 liters without any problem.

The subject of compressor-jet combinations could make a 30-minute talk in and of itself. Generally, there are high-, middle-, and low-power compressors, and Steve Newman has done a lot of work on that subject, to identify the higher power nebulizers.[1] If you need to nebulize a more viscous solution, such as tobramycin or certain antibiotic solutions, Newman showed that you need the most powerful compressor.

The problem you mentioned is important; when manufacturers specify the compressor output they always do it with an open output and no resistance attached. The *real* question is, "What is the flow rate given a certain resistance?" And the answer differs among the various nebulizers. That's the other variable that comes into play. You have to test the compressor with the particular nebulizer that's going to be used, because the *nebulizers* differ in resistance as well, which, in turn, will determine the flow rate. But it's clear that with less viscous solutions, such as the bronchodilator solutions, you can use the lower flow rate and get away with it, whereas with higher-viscosity solutions you cannot.

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MacIntyre: You showed a lot of variability in the lung deposition data. A lot of it is, of course, due to differences in the designs of the systems, but how much of it might be related to other factors, such as nonstandardization of the flow rates and the tidal volumes and things like that, which also affect lung deposition?

Rau: I would certainly answer that, first, the conditions of testing—the fill volume, the flow rate, the solutions being tested—definitely influence the data you get. There's been some interesting data from Hollie et al[1] and Alvine et al[2] on nebulizer performance variability, both within the same nebulizer model and between models, that showed unacceptably large variability. They attributed it to poor quality control in the nebulizers' production processes—the plastic injection and flow molding processes. That's outside my expertise, but they did, under the same conditions, find a large degree of variability within the same nebulizer model and among nebulizers.

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Aerosol Delivery Through an Artificial Airway

Neil R MacIntyre MD FAARC

Introduction
Natural Versus Artificial Airways
Assessment of Aerosol Delivery Through Artificial Airways
In Vitro Measurements
In Vivo Assessments
Comparison of Aerosol Delivery With and Without an Artificial Airway
Factors Important in Optimizing Delivery Through an Artificial Airway
Ventilation Pattern and Timing
Carrier Gas Properties
Nebulizing Devices
Circuit Properties
Ideal System
Intra-Airway Delivery Systems
MDI Nozzle Extender
Intra-Airway Aerosol-Generating Catheter
Summary

For both lung and systemic diseases, aerosol delivery of drugs into the lungs can often offer substantial advantages over other routes of administration. In the intensive care unit, however, the artificial airway can be a substantial barrier to aerosol delivery, so clinicians must pay careful attention to the ventilator pattern, the delivery gas humidity/density, the device characteristics, and the circuit/tube properties. When those are optimized, aerosol delivery from a nebulizer or metered-dose inhaler and through an endotracheal tube can begin to approach that seen in a nonintubated patient. Novel approaches, such as generating the aerosol within the airway, offer the opportunity to greatly increase deposition efficiency and focal drug targeting in intubated patients. *Key words: nebulization, nebulizer, aerosol, artificial airway, endotracheal tube.* [Respir Care 2002;47(11):1279–1285]

Introduction

Medication delivery into the airways of intubated patients can offer substantial advantages over parenteral or oral administration routes.[1–3] For medications targeted at lung diseases (Table 1), a higher therapeutic index can be achieved with drugs delivered directly to the site of intended action, with little or no systemic exposure. The lung can also be a useful portal for medications designed for systemic targets, because drugs that can easily pass through the alveolar-capillary interface (eg, insulin) can be exposed to a large lung surface area in contact with the entire cardiac output.

Effective aerosolized medication delivery into the lungs of intubated patients depends on many of the same factors important in nonintubated patients:[4] efficient device output, small particle size, low-velocity gas flow, large inspired volume, and breath-hold at end inspiration. The

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Table 1. Medications Suitable for Nebulization to an Intubated Patient

Lung Targeting
· Bronchodilators (beta agonists, anticholinergics)
· Steroids
· Vasodilators (nitric oxide carriers, prostacyclin)
· Anti-inflammatory agents
· Antibiotics
· Mucolytics
· Surfactants
· Genes
Systemic Targeting
· Insulin

intubated patient, however, offers additional challenges: the artificial airway is a different geometry than the natural airway; the aerosol delivery system is generally attached to the ventilator circuit in which heat, humidification, and bias gas flows may be present; pressure gradients down the airways are different than during spontaneous breathing; and the required mechanical ventilatory pattern may not be ideal for aerosol delivery. In this paper I review these issues and examine some novel design concepts that may help optimize aerosol delivery.

Natural Versus Artificial Airways

Figure 1 shows the normal upper-airway anatomy.[5] Note that in the nonintubated patient, aerosols generated outside the mouth must traverse a $> 90°$ course, with several points of sudden narrowing, to reach the lower airways. These physical attributes provide a critical normal barrier function for the lungs and are the reason that, even under the best of conditions, efficient aerosol delivery in a nonintubated patient can be a difficult clinical challenge.

The presence of an artificial airway (see Fig. 1) can additionally impair aerosol delivery. Typical endotracheal tubes (ETT) considerably narrow the passage an aerosol must traverse to enter the lungs. Moreover, the opening of the artificial airway into the trachea may be angled such that gas and aerosol flow is aimed at the trachea wall. Particle velocity and turbulence are thus increased, which promotes aerosol deposition along the walls of the tube and at the airway opening. Although some of the natural upper-airway "choke points" (eg, vocal cords) are eliminated with a smooth-bore tube, the build-up of secretions inside an artificial airway can add focal obstructions that increase tube deposition. Another aspect of the presence of an artificial airway is that it prevents the aerosol from contacting the oral mucosa or gastrointestinal tract, so systemic absorption from those surfaces is eliminated.

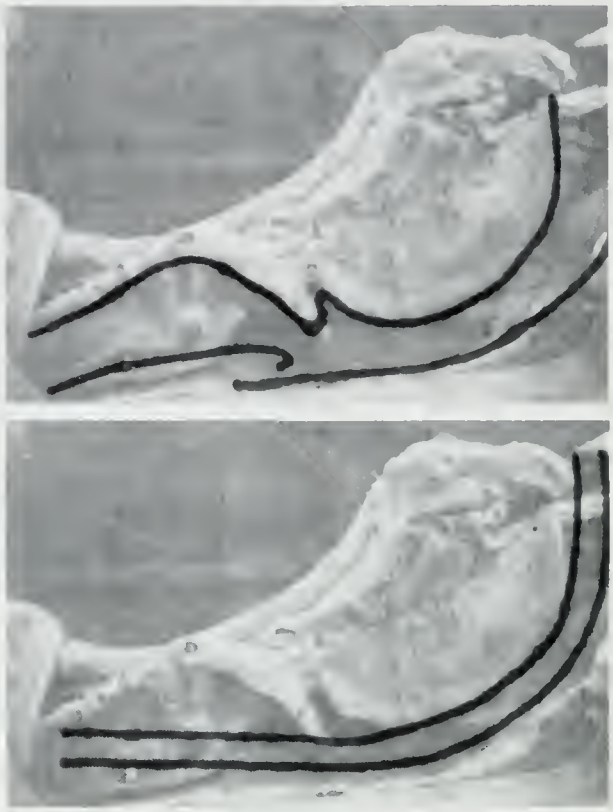

Fig. 1. Sagittal sections of the upper airway. In the lower panel the contour of an endotracheal tube placed through the vocal cords is superimposed. (From Reference 5, with permission.)

Assessment of Aerosol Delivery Through Artificial Airways

In Vitro Measurements

Table 2 summarizes lung modeling studies of the performance of aerosol-generating devices for use with artificial airways.[6–17] For nebulizers, deposition rates have ranged from as low as 1.2% to as high as 43%.[6–12] This variability seems largely explained by differences in techniques (reviewed below) and underscores how aerosol delivery through the artificial airway is particularly sensitive to those differences.

In vitro studies of metered-dose inhaler (MDI) performance have also shown considerable variability, with deposition rates of 5–39% (see Table 2).[6,10,13–17] Again, technique factors are probably responsible. Although early in vitro studies suggested MDI performance may have been better than nebulizers, later studies showed that when nebulizers and MDIs are used optimally their performance appears to be more similar.[10]

Table 2. Aerosol Deposition Through Artificial Airways: In Vitro Studies

Author	Type*	Deposition (%)	Comments
Fuller[6]	Jet	1.2	
O'Doherty[7]	US	3.1–5.4	Depends on inspiratory time, circuit design
O'Riordan[8]	Jet	3–37	Depends on device, ventilation pattern, volume fill, humidity
Thomas[9]	US	3–22	Depends on device, ventilation pattern, circuit design
Diot[10]	Jet	43	Dry circuit, long inspiratory times
Kemming[11]	US	25–31	Emitted through tube; volume-controlled ventilation better than pressure-controlled ventilation
Harvey[12]	Jet and US	2.3–5.3	Jet more than ultrasonic
Fuller[6]	MDI	5.6	—
Rau[13]	MDI	5–32	Spacer improved deposition
Diot[10]	MDI	15–25	Spacer improved deposition
Everard[14]	DPI	20	—
Fink[15,16]	MDI	4.9–39	Depends on humidity, propellant, inspiratory time, spacer

*All devices are in-line
US = ultrasonic
MDI = metered-dose inhaler
DPI = dry powder inhaler

In Vivo Assessments

Table 3 summarizes in vivo assessments,[18–24] which are generally done using radiolabeled aerosols. Again, considerable variability is seen in both nebulizer and MDI performance (deposition rates of 2.2–30.6% and 1.7–11%, respectively), and again this variability seems largely due to technique factors. Measuring serum or urine concentrations after aerosol administration can be a useful way to assess how much of an aerosol reached the systemic circulation. A recent study that included urine assays of albuterol showed that with an MDI-with-spacer system, urine albuterol was 38% of the administered dose, as compared to 16% when given via nebulizer.[22]

In comparing in vitro and in vivo measurements, a number of considerations must be taken into account.[25] In vitro tests may overestimate delivery because they are often performed in nonhumidified circuits, the tubes are clean and well positioned, and particles that would be exhaled in vivo are trapped by the in vitro system. In vitro analysis also ignores regional deposition. In vivo scanning may underestimate delivery because of tissue attenuation of the signal and systemic absorption of the radiolabeled material before scanning is complete.

Table 3. Aerosol Deposition Through Artificial Airways: In Vivo Studies

Author	Type*	Deposition (%)	Comments
MacIntyre[18]	Jet	2.9	—
Fuller[19]	Jet	2.5	—
Thomas[20]	Jet	2.2	—
O'Riordan[21]	Jet	30.6	Dry circuit, tracheostomy
Harvey[12]	Jet	2.2–3.0	Spacer improved deposition
Marik[22]	Jet	16	Urine recovery of drug
Harvey[23]	Jet/US	2.3–5.3	US better than jet
Fuller[19]	MDI	6	No spacer used
Fuller[24]	MDI	1.7–11	Spacer in inspiratory circuit improved deposition
Marik[22]	MDI	9–38	Urine recovery of drug; spacer in inspiratory circuit improved recovery

*All devices are in-line
US = ultrasonic
MDI = metered-dose inhaler
DPI = dry powder inhaler

Comparison of Aerosol Delivery With and Without an Artificial Airway

The general impression is that aerosol deposition through an ETT is less efficient than through a natural airway, but that perception is based largely on comparing the data (noted above) from intubated models or patients to data obtained in separate studies in nonintubated patients. A few "head-to-head" studies do exist, however. Our 1984 study, which used the same radiolabeled technique in both intubated and nonintubated subjects, suggested that the ETT substantially reduced the amount delivered by a nebulizer system.[18] In a study comparing MDI delivery, serum concentrations per puff of albuterol were also lower in the intubated patient than in the nonintubated patient.[26]

Physiologic (bronchodilator) responses to intubated and nonintubated techniques also suggest that the artificial airway reduces delivery. Specifically, several studies have shown that additional puffs from an MDI or additional bronchodilator dose from a nebulizer are required to obtain physiologic effects comparable to those seen in nonintubated subjects with standard dosing.[27–29]

The bottom line is that using traditional approaches to nebulization and MDI therapy in intubated patients does seem less efficient than delivery to a nonintubated patient. However, there are a number of factors that can be optimized to enhance aerosol delivery through the ETT, and when those are all used it is conceivable that delivery through an artificial airway can start to approach that through a nonintubated airway.

Factors Important in Optimizing Delivery Through an Artificial Airway

Ventilation Pattern and Timing

In lung model studies, aerosol delivery was substantially improved by slowing inspiratory flow or increasing the percent of time spent in inspiration.[7,9,16,30–33] For example, delivery to a lung model increased 50–66% as inspiratory flow was decreased from 50 L/min to 22.5 L/min and increased over 3-fold when the inspiratory time fraction was increased from 20% to 50%. Larger tidal volume also improves deposition, but it should be recognized that there are clinical trade-offs involved: slower inspiratory flow, longer inspiratory time, and larger tidal volume may result in air trapping or lung overdistention, and those breathing patterns can be uncomfortable for the patient.

Other ventilatory pattern issues are also important. Timing aerosol delivery to inspiration increases efficiency because less aerosol is wasted during expiration. Patient effort during ventilator-assisted breaths may also enhance delivery.[2] Presumably this is because of larger pressure gradients in the distal airways than in the proximal airways during active ventilatory effort.

Carrier Gas Properties

There are 2 important properties of carrier gas relative to aerosol delivery: humidity and density. Humidity can prevent the evaporation of some aerosol particles or greatly increase the particle size of other aerosols.[10,16,25] Inappropriate particle sizing from humidity-induced changes can substantially hamper lung deposition and may explain why deposition in earlier in vivo assessments of nebulizer performance in humidified ventilator circuits was so poor. A number of recent studies showed that a dry carrier gas can as much as double aerosol delivery to the lung.[10,16] A trade-off obviously exists, however: though short treatments involving brief periods of dry gas delivery may not have much clinical consequence, if the treatment period lasts a number of minutes airway desiccation can be a serious problem.

Gas density can also affect aerosol delivery characteristics. Specifically, turbulent flow increases particle impaction onto surfaces, thereby reducing distal delivery.[34–36] Reducing gas density reduces turbulence. A number of studies have clearly demonstrated that using the low-density gas heliox (an 80% helium, 20% oxygen mixture) improves deposition in lung models by as much as 50%.[34–36] Heliox, however, should not be used as the power-gas for a nebulizer, because a low-density power-gas substantially reduces nebulizer output.

Nebulizing Devices

A nebulizer is characterized by both its particle size generation and its output. Efficiency can also be affected by the "dead volume," which is the amount of liquid remaining in the nebulizer (and thus wasted) at the end of nebulization.

In nonintubated patients the "respirable range" of aerosol particles is 1–5 μm.[4] Particles larger than 5 μm deposit in the pharynx and upper airways. Particles smaller than 1 μm are often exhaled. In the presence of a narrow ETT, particles in the range of 1–3 μm appear to be more efficiently delivered and thus should be the target particle size for devices used with intubated patients.[1–3,30]

Clinically available nebulizers for use with intubated patients differ markedly in their output and particle size properties, depending on the device's design and the properties of the liquid being nebulized.[8] The 2 most commonly used designs with ventilator circuits are the jet nebulizer (gas jetted across a liquid to produce aerosol particles) and the ultrasonic nebulizer (ultrasonic energy breaks up a liquid/gas interface to produce aerosol particles). In general, outputs from either device can range from < 100 to

several hundred microliters per minute and the mass median aerodynamic diameter can range from < 2 to up to 5 μm. There is thus considerable variability among manufacturers, and the drug delivery performance of one system cannot be extrapolated to the performance of another.

Some jet nebulizers are also affected by the drive pressure. This is important because continuous nebulization is often powered by wall gas (50 psi), whereas intermittent nebulization (timed to inspiration) may be powered by the ventilator (drive pressure < 15 psi), and these lower drive pressures may reduce output in some systems.

In contrast to nebulizers, MDIs supply only a few microliters per puff (although the drug concentrations are usually higher than nebulizer solutions). Multiple puffs may thus be required to match the efficacy of a nebulizer. MDI particle size distribution is comparable to that of a nebulizer, but particle velocity exiting the MDI nozzle can be substantial, which is the major reason ventilator circuit chambers (see below) are needed with MDIs. Also, each MDI is linked to a single drug formulation. In general, nebulizers can supply much larger volumes and a wider variety of aerosols than MDIs, but are generally more expensive and cumbersome.

Circuit Properties

A number of circuit properties affect aerosol delivery through an ETT or an artificial airway. Artificial airway tube diameter, length, bends, obstructions, and the exit angle at the opening into the airway all affect flow properties and the potential for aerosol impaction before reaching the target in the lung.

Device location in the circuit is also important. For continuous nebulization, placing the device close to the patient Y-piece causes considerable aerosol waste during expiration, especially if a ventilator circuit bias flow is present.[15] In contrast, if the nebulizer is placed in the inspiratory circuit away from the patient Y-piece, nebulization during expiration may largely serve to fill and charge the inspiratory circuit, with little loss during expiration.

With an MDI it is particularly important to use a holding chamber in the inspiratory circuit to slow the particle velocity and thereby permit adequate delivery.[10,13,22,24] Indeed, with an MDI almost no delivery occurs using direct injection into an elbow adapter.

Circuits and tubes are often made of plastic, the surface of which can have a static charge[4] that can attract aerosol particles and thus reduce aerosol delivery. Priming the system with an aerosol before delivering the treatment aerosol may bind and thus neutralize the static charge sites and thus enhance delivery. Washing the circuit and tube in detergent or using tubing that does not hold a static electric charge can also help enhance aerosol delivery.

Ideal System

The ideal aerosol delivery system would have:

1. A patient-triggered ventilation pattern, slow inspiratory flow, long inspiratory time, large tidal volume, and an end-inspiratory pause
2. An unhumidified and very-low-density carrier gas
3. An aerosol generator with a very high output, low dead volume, and particle generation in the 1–3 μm range
4. A circuit that is wide bore, smooth, without static charge, properly centered, and that facilitates low-velocity particles

With all of those factors affecting aerosol delivery it is not surprising that so much variability is seen in existing studies. As aerosol systems approach the ideal, aerosol delivery through an ETT may be substantially improved and near that seen with the nonintubated patient.

Intra-Airway Delivery Systems

Even under the best of circumstances, with systems that approach the efficiency seen in nonintubated patients, it is still clear that aerosol delivery into the lungs will be unlikely to exceed 25–40%. Though that may be acceptable for many inexpensive drugs (eg, steroids or bronchodilators), that inefficiency may be unacceptable for more expensive drugs. For delivery of expensive drugs, devices to place the aerosol directly into the lungs have been explored. Two such devices are the MDI nozzle extender and the intra-airway jet nebulizer catheter.

MDI Nozzle Extender

This is a relatively straightforward concept: the nozzle of the MDI is made long enough to traverse the length of the artificial airway.[36,37] The plume of aerosol is thus introduced directly into the trachea. The extender must be < 1 mm in diameter to preserve appropriate particle sizing and output at the extender tip. This unfortunately creates a high-velocity aerosol stream in close proximity to airway tissue.[37] Substantial tracheal/carinal deposition can occur (as much as 70% of the delivered aerosol), and the high-velocity gas has been shown to create airway ulcerations in animals. Flaring the tip of the extender can help reduce the exit velocity and decrease tracheal deposition, but it is not clear if these safety issues can be sufficiently overcome to allow this concept to be used clinically.

Intra-Airway Aerosol-Generating Catheter

Our group has developed an intra-airway aerosol generator that consists of a small-diameter (1 mm internal diameter) catheter with a central lumen surrounded by peripheral lumens (Fig. 2).[38,39] The liquid to be nebulized

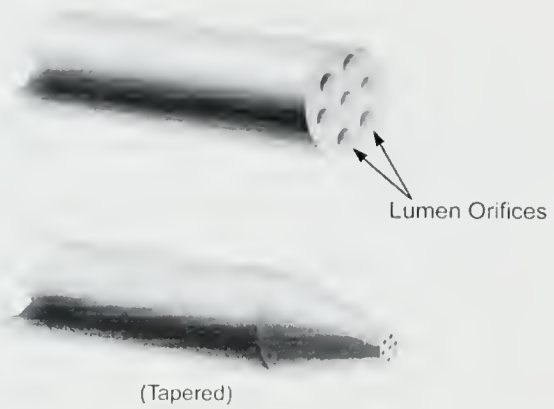

Fig. 2. A multilumen, small-diameter catheter designed to produce a fine aerosol at the tip. Liquid is delivered through the central lumen and gas is jetted through the peripheral lumens.

is delivered through the central lumen as the power-gas is delivered through the peripheral lumens, which nebulizes the liquid. The catheter tip can be positioned at the distal end of an artificial airway or guided (via bronchoscope) to selected airway positions. Because upper-airway anatomy is bypassed with this technique, larger particle sizes (up to 10 μm) can conceivably be delivered effectively to the major airways.[39]

Lung model studies using radiolabeled liquid found that virtually all of the liquid passing through the center lumen can be nebulized. However, the device produces a substantial aerosol velocity, so substantial tracheal/carinal impaction is observed. Nevertheless, the lung model studies showed a several-fold higher distal lung, parenchymal deposition than standard nebulization techniques. A final point with regard to this system is that, because it involves gas delivery into the lung (although generally $<$ 1 L/min gas flow is required), pressure monitoring must be part of any such system.

In the future, other nebulizing techniques that do not use gas or impart aerosol velocity may lend themselves to miniaturization and placement within the airways. Such systems, especially if particle size could be tightly controlled, can be envisioned to not only provide extremely efficient whole-lung delivery but also very targeted aerosol delivery to selected lung regions.

Summary

The artificial airway can be a substantial barrier to aerosol delivery into the lungs. However, with careful attention to the ventilator pattern, the delivery gas humidity/density, the device characteristics, and the circuit/tube properties, aerosol delivery from standard nebulizers or MDIs can begin to approach that seen in the nonintubated patient. Novel approaches to generating the aerosol within the airways offer the opportunity to greatly increase deposition efficiency and focal drug targeting.

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Discussion

O'Riordan: Thank you for a very nice presentation. I want to comment about our experience with the modeling of mechanical ventilation. You presented the fact that we modeled a very good aerosol delivery, but we also modeled a very bad delivery. In terms of practical issues for the clinician, probably the easiest thing to do is to pick the right nebulizer. The one we used was a nuclear medicine nebulizer called the Aerotech, which is comparatively expensive, and we reserve it for antibiotics and nonbronchodilator therapy at our institution. That's probably the straightforward way of optimizing delivery. The second relates to the fact that it has to be cycled with inspiration for efficiency. And for that, to keep it practical, you have to keep the fill volume small; otherwise, the treatment time becomes very prolonged. Finally, about the humidification; we simply turn off the humidifier temporarily. Those are the "big 3" things a clinician can do to optimize delivery. If you don't do those things you very easily get the very bad delivery that has been seen in some reports.

MacIntyre: How about heliox?

O'Riordan: We haven't used it. I would prefer to defer to Jim Fink or Rajiv [Dhand], who have more data on that.

Dhand: Certainly, administration of drugs with heliox is a very interesting possibility, and Jim [Fink] has done excellent work on that. As you point out, we can see an almost 50% increase in aerosol delivery, given the proper technique. A recent study from the University of Chicago looked at bronchodilator responsiveness in emergency room patients and found much better spirometric response when they nebulized with heliox rather than oxygen.[1]

We also need to consider that aerosol delivery to the critically ill, intubated patient poses several unique problems. With an ambulatory patient you can provide advice, and then the onus of drug delivery is on the patient. But in the intensive care unit the patient is fairly helpless and so the onus of drug delivery is on the clinician or the respiratory therapist, and it

behooves us to use the most appropriate technique to ensure that the maximum amount of drug is delivered. From a scientific standpoint it is interesting that drug is delivered directly into the lungs in intubated, mechanically-ventilated patients, and there is no oropharyngeal or gastrointestinal deposition to muddy the picture. Therefore, drug that appears in the plasma or is excreted in the urine is a very good reflection of what was deposited in the lung.

Another factor to consider in these patients is body position. We normally talk about aerosol deposition in ambulatory patients, who inhale in the erect posture, whereas mechanically-ventilated patients are often flat on their backs or semi-recumbent. That difference in posture definitely influences the pattern of aerosol deposition. Finally, I was interested in your data about the intratracheal jet. I would actually think of it the other way around; that is, I think this could be an excellent device to target the airway rather than the alveoli. Here you could have a device to specifically treat airway disorders without having deposition in the alveoli. I think that raises some very interesting possibilities.

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Dunne: The take home message that I got, very clearly, was that lung deposition is extremely technique-dependent, especially with the intubated patient. Can you expand on that? I think you alluded to it toward the end of your presentation, that aerosol therapy in general, to be successful, is heavily technique-dependent across the spectrum. I don't want the message to be only for the complex patient; rather, there's a lot of aerosol therapy done outside the hospital that I suspect is not done optimally.

MacIntyre: Patrick, I think you are exactly right. I think the points I raised here about the intubated patient are often relevant to the nonintubated patient as well. The lung was "designed" with bends, angles, and obstructions to keep particles out, so for us to overcome those obstacles requires some thought. These techniques—slow flow, deep breath, long inspiratory time, and breath-hold—are all applicable to both intubated and nonintubated patients. But as Rajiv [Dhand] said, with the intubated patient we have the ability to control those things, whereas with the at-home patient we have to depend on them to *learn* the right technique. And that's a different set of problems.

Stenzler:* Considering Joe's [Rau] presentation, which showed that nebulizers produce different particle sizes depending on how you use them, do you think that the flow rate and driving pressure with a spontaneously breathing patient should be different than that with an intubated patient? Maybe we need a different technique for intubated patients with the same devices.

MacIntyre: Alex, I think we probably do. We have different airway geometries to deal with in intubated and nonintubated patients, and presumably there would be different particle sizing optimizations and different flow patterns that would be better in one situation than another. For instance, with particle size, the smaller the particle the better the lung deposition, but less material is going in because the particles are smaller, and there's a tendency to exhale very small particles back out. So it's not a free lunch just by making the particles smaller, but smaller particles are probably more important for the intubated patient, just because of the challenge of getting through the tube. Tom, do you have a comment on that?

O'Riordan: I think you have to use small particles. Otherwise you have to worry about the humidity of the system making the particles bigger. Also, the positive pressure results in more turbulence, so even if you use a small particle that would deposit peripherally in a normal, spontaneously breathing subject, the turbulence will substantially increase central deposition in an intubated patient. So I think you *will* get adequate airway deposition, even with a small particle.

Smaldone: I think your talk very nicely summarized how we've learned about the complexities of ventilated aerosol delivery, and it's really an offshoot of basic nebulizer testing in a much more complicated system. I think that the real problem is that we're chasing a moving target, because we're not working closely with ventilator manufacturers. Ventilators are not manufactured with aerosol delivery in mind. And it's getting worse; we've done some follow-up studies along the same lines as what you presented, and it's getting harder with newer ventilators to deliver aerosols with any kind of control.

So the way I would summarize this is that it's almost impossible to control aerosol delivery with a mechanical ventilator. It's difficult, for instance, to get respiratory therapists to deliver aerosolized antibiotics in the way we know they need to be delivered (based on the variables Tom O'Riordan summarized) to get them into the lung in the right amounts. It's hard to get people to do it, even on your own turf. So I think the problem here is lack of control. Setting standards and working with device manufacturers are critical, and it's never more demonstrable than with ventilators, because the newer ventilators are

*Alex Stenzler RPFT, VIASYS Healthcare, Yorba Linda, California.

getting even worse, in terms of their ability to deliver aerosols.

Dolovich: I want to raise the issue of patient population. You talked mainly about adult delivery. I wonder if you want to comment on aerosol delivery to neonates.

MacIntyre: Myrna, I think that's a very understudied area. There are some reports dealing with pediatric delivery and pediatric endotracheal tubes, but there's not as much as in the adult literature. Bruce, can you help me?

Rubin: There are some fairly good pediatric data; there are virtually *no* neonatal data. Neonatologists are very busy intensivists for very small people, who very much like putting as much as possible down into endotracheal tubes, because they don't have access to big lines in veins. And many of them don't have the time to study what goes down those tubes, so we'll find the most *amazing* things nebulized in the neonatal nursery, primarily because "we've got to get something to the patient." So it's wide open in terms of what needs to be studied.

MacIntyre: What kind of things are you talking about?

Rubin: You name it; everything from surfactants, obviously, to bronchodilators to pulmonary hypertension medications to corticosteroids to mucoactive agents to whatever else happens to be helpful.

MacIntyre: Is there any room for gas in this patient's lung?

Dennis: There *are* no lungs!

Rubin: It's done out of desperation, and the airway seems a very accessible site, because so often you have difficulty taking care of other bits of the babies, and the babies *usually* have pulmonary problems, but data are very few.

Fink:* You started off with the statement that the endotracheal tube seems to be a barrier to aerosol delivery. You presented 3 slides from our models[1,2] in which we found that the endotracheal tube accounted for less than a third of the aerosol lost between the MDI adapter and the patient's lungs, with greater losses at the Y-piece and right-angle connector. This was true with both wet and dry circuits and with use of heliox. That suggests that the endotracheal tube is less of an aerosol barrier than other factors.

When we studied serum albuterol levels in intubated versus nonintubated patients we found that intubated patients had only 70% of the serum levels per puff as that of the nonintubated patients.[3] But the intubated patients were receiving 95% humidity at body temperature and the nonintubated patients were inhaling in an air-conditioned lab, so the 30% lower aerosol delivery may have been related more to the higher humidity in the ventilator circuit than to the losses in the endotracheal tube.

As to what constitutes an ideal for aerosol delivery during mechanical ventilation, I agree that the limitations of current technology induce us to control the ventilation very closely, for optimal deposition. However, I believe that what we really need to look forward to are systems that efficiently deliver aerosol to the lung using ventilator parameters that are consistent with good clinical practice. Then we wouldn't be tempted to change how we ventilate patients and potentially put them at risk from low humidity or high inspiratory-expiratory ratios to get a decent dose of drug into the lungs.

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MacIntyre: Fair point.

Barry: You concentrated on intubated patients on intermittent positive-pressure ventilation. I wonder if you can comment on aerosol delivery to patients on face mask CPAP [continuous positive airway pressure], such as for chronic obstructive pulmonary disease, and on nebulizer use with high-frequency oscillation.

MacIntyre: I would imagine that aerosol deposition through a face mask with a continuous positive airway pressure system would have many of the issues associated with aerosol delivery through mouthpieces and the like. High-frequency oscillation is an interesting question. I talked to Alex [Stenzler] about how best to deliver an aerosol during high-frequency oscillation, in which there's a continuous flow of gas being delivered into the circuitry, and it's being oscillated. How to get an aerosol down that kind of setup is a fascinating problem. You can put a nebulizer in the circuit, and you can get aerosol to go into the lung, but I think the parameters and the way to optimize that is largely unknown. We just rig it up and do it! Alex, can you help me here? Are there more specific data on oscillator aerosol delivery?

Stenzler: After I've finished I'll have Jim [Fink] talk. He presented a poster, at the *CHEST 2001* conference, on aerosol deposition with high-frequency oscillation.[1] A few years ago we did a few pilot studies using the

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catheter. I think your data on conventional ventilation had about 80% retention? And I think when we did the catheter with high-frequency oscillation we had a 95% retention in the lung. For the same reason that it's difficult to get aerosols into the lung, if you generate them within the lung it's hard for them to leave. So we had very high deposition in an animal model.

REFERENCE

1. Fink JB, Barraza P, Bisgaard J. Aerosol delivery during mechanical ventilation with high-frequency oscillation: an in vitro evaluation. Chest 2001; 120(4 suppl):277s.

MacIntyre: Yes. This is obviously very preliminary stuff, and I think it's a fascinating field, but it has very little data. Where to put the nebulizer, what the particle size should be, and how to set it up is largely unknown. As Alex said, we did try. We've just done a couple of anecdotal experiments, looking at using the catheter device, and it does seem to help.

Stenzler: And Jim addressed that in that recent poster session.

Fink: Yes, we compared a prototype of the Aeroneb Pro to a couple of jet nebulizers, placed in line with a high-frequency oscillator. We found that in both pediatric and adult settings we had greater than 3-fold better delivery of albuterol in vivo. We delivered 24% of the dose past the tip of the endotracheal tube in vitro.[1]

REFERENCE

1. Fink JB, Barraza P, Bisgaard J. Aerosol delivery during mechanical ventilation with high-frequency oscillation: an in vitro evaluation. Chest 2001; 120(4 suppl):277s.

MacIntyre: This was just putting the nebulizer in the continuous flow circuit?

Fink: The nebulizer was placed in the inspiratory limb immediately before the Y-piece.

O'Riordan: I want to go back to the neonatal issue. I think neonatal mechanical ventilation is very different from pediatric ventilation, mainly because of the high gas flows used with neonatal systems. A great deal of the aerosol is simply washed out by the bias flow in the system. We used some of our modeling data (using parameters that delivered 40% of the nebulizer dose to adults) in a neonatal model, and it delivered about 1%.[1] Though neonates are obviously a lot smaller, so you don't need as much drug, I think it should be appreciated by anyone who wants to deliver drugs to a neonate that it is a completely different system, and very few of the adult and pediatric ventilation data are applicable to neonates.

REFERENCE

1. O'Riordan TG, Kleinman LI, Hughes K, Smaldone GC. Predicting aerosol deposition during neonatal ventilation: feasibility of bench testing. Respir Care 1994;39(12): 1162–1168.

Rubin: That being said, I think Myrna [Dolovich] will probably present some of the data that she generated on the neonatal stuff.[1] I think that's still some of the best work. Regarding high-frequency oscillation, though, there is some unpublished data from Malcolm King and his group that's been presented several times in abstracts but I haven't seen it in print yet. It shows that patients inhaling mucoactive agents such as dornase alfa get much better deposition when they do it in conjunction with high-frequency chest wall oscillation, as opposed to doing it before or after using *The Vest* [high-frequency chest wall oscillation system], which may or may not be applicable to some of the studies related to oscillation.

REFERENCE

1. Fok TF, Monkman S, Dolovich M, Gray S, Coates G, Paes B, et al. Efficiency of aerosol medication delivery from a metered-dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1996;21(5):301–309.

Geller: I want to thank Myrna for bringing up the pediatric issue, because that's what got me interested in aerosols in the first place. In the late 1980s we discovered that we were getting less than 1% of the aerosol through the ventilator circuit and endotracheal tube and into the baby's lungs. I read a few years ago that the neonatal group at Stony Brook came up with an ultrasonic device that delivered about 45% to guinea pig lungs; they were trying to deliver superoxide dismutase. I haven't heard much from that group since, but that was an incredibly high amount. Have you heard any follow-up on that?

O'Riordan: That was a different group at Stony Brook.[1] The problem with neonatal systems is the very high bias gas flow relative to tidal volume. It was my understanding that by using a breath-actuated system they were able to overcome that problem. The device was ultrasonic, so they weren't depending on an external flow of gas to get the aerosol in.

REFERENCE

1. Langenback EG, Davis JM, Robbins C, Sahgal N, Perry RJ, Simon SR. Improved pulmonary distribution of recombinant human Cu/Zn superoxide dismutase, using a modified ultrasonic nebulizer. Pediatr Pulmonol 1999;27(2):124–129.

Smaldone: I'm not really familiar with that device. Tom [O'Riordan] knows more about it; he did a study with rabbits,[1] and I think that agrees with the work that Myrna's done. I think it's appropriate to mention this because in neonates the ventilator is a critical issue, as Tom alluded to, and modern ventilators for adults are becoming more like neonatal ventilators, with constant flows and that sort of thing. But for neonates the endotracheal tube is one of the major impediments to aerosol delivery. In adults I don't think the tube is really a big

issue; it's important but we can deal with it. With neonates, even if we solve the ventilator problem the tube problem remains. We had a lot of trouble getting aerosol through the tube in our neonatal model. The oscillator may solve the ventilator problem in neonates, for aerosol delivery in particular. I think the tube remains the biggest issue.

REFERENCE

1. O'Riordan TG, Kleinman LI, Hughes K, Smaldone GC. Predicting aerosol deposition during neonatal ventilation: feasibility of bench testing. Respir Care 1994;39(12): 1162–1168.

Geller: Perhaps there is a different way of thinking about this. Since there's so much difficulty in nebulizing drugs to the lung of a ventilated patient, what about changing the formulation so that drug spreadability is increased? If you can get it as far as the trachea, it would just spread peripherally from there. For example, maybe a surfactant-like substance could increase spreadability. I don't know if that's even possible with some drugs, but in thinking about targeting the lung, that may present interesting possibilities.

Dolovich: We have done experiments with rabbits, in which we added surfactant to the drug solution, and it did improve delivery. But I want to comment again on neonates. We've done a couple of studies in the neonatal group.[1,2] One of the other factors that's important is the concentration of the aerosol. If you can concentrate the aerosol cloud in a holding chamber, you have a greater chance of delivering more. I say that because we've compared nebulizer to MDI-plus-spacer, and the nebulizer delivery is very weight-dependent—that is, tidal-volume-dependent—whereas the MDI is not. Deposition from the MDI is greater, more variable, but not dependent on tidal volume. I think it's mainly because we're presenting a different amount of drug to the endotracheal tube.

REFERENCES

1. Fok TF, Monkman S, Dolovich M, Gray S, Coates G, Paes B, et al. Efficiency of aerosol medication delivery from a metered-dose inhaler versus jet nebulizer in infants with bronchopulmonary dysplasia. Pediatr Pulmonol 1996;21(5):301–309.
2. Dolovich M. Rationale for spacer use. Pediatr Pulmonol 1997; Suppl 16:184–185.

Dhand: Myrna, I'm hoping you can provide some insight into one question that has been raised. With the small neonatal lung, when you use a metered-dose inhaler, you're giving a large dose of propellant and surfactant along with the drug. How does the neonatal lung respond to that propellant?

Dolovich: We haven't looked at that, specifically. There was only one abstract in the literature that I could find in which the F_{IO_2} (fraction of inspired oxygen) dropped after 2 doses. So that sort of sent the flags up. I think we need a study to see if propellant inhalation is an issue in infants. In adults the levels decrease almost to baseline with the next breath, but that may not necessarily happen in neonates.

Assessing Nebulizer Performance

Myrna B Dolovich PEng

Introduction
In Vitro Tests
Testing for Variability in Manufacturing Between Units
Temperature Change in the Reservoir Solution During Nebulization
Nebulizer Output
Particle Size of the Nebulized Aerosol
Measuring Drug Output Under Simulated or Actual Breathing Conditions
In Vivo Testing
Summary

The quality of the aerosol generated by a nebulizer system is a function of its design, operating parameters, and the drug formulation to be aerosolized. The aerosolized drug dose inhaled from a nebulizer is determined by the patient's breathing pattern. The site of deposition of the aerosol in the lung is primarily influenced by the inspiratory flow rate and additionally by the nature of the lung disease. Thus, tests of performance that incorporate these different variables will provide data that give a better understanding of overall nebulizer performance. As discussed in this paper, a number of in vitro and in vivo laboratory tests can be undertaken to measure the characteristics of the delivery system as well as the quality and quantity of the aerosolized drug provided. With this information one can estimate the dose of drug that will be inhaled and deposited below the larynx. The accuracy of these predictions can additionally be improved with the use of breath simulators and standard breath patterns. Breath monitors that capture and feed actual patient breathing patterns into the simulator to mimic nebulizer operation during actual patient use further increase the accuracy of dose estimation. With the vast number of nebulizers available and also in development, a comparison of information obtained from different nebulizers is key in making an informed decision when selecting an aerosol delivery system that can provide an efficacious dose of a particular drug to a specific patient population. *Key words: liquid nebulization, aerosol dose, particle size, breath simulation, nebulizer, aerosol.* [Respir Care 2002;47(11):1290–1301]

Introduction

The efficiency of delivery of aerosolized medications varies among nebulizer systems.[1] Differences in the amount of drug aerosolized and the respirable dose provided depend on a number of factors and can be considerable.[2] This may result in different clinical effects, particularly if the aerosol delivery efficiency is poor in comparison to other drug delivery methods or other nebulizers.[3,4] Similarly, the performance characteristics of a nebulizer used with one type of drug may be different when used with other categories of drugs and potentially with generic formulations of a particular drug. Thus, it would be prudent to measure the output characteristics of a drug from a number of neb-

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ulizer delivery systems prior to recommending the use of a specific system or systems for the drug.

In Vitro Tests

In vitro performance assessment of a new nebulizer to demonstrate similarity to an already-marketed device is a regulatory requirement under section 510(k) of the Food, Drug, and Cosmetics Act and is required before regulatory approval.[5] Only with that approval in place is a company permitted to sell the device. The types of measurements discussed below are also used by manufacturers to assure quality control of marketed products. Nebulizer performance assessment is similarly useful to the end user, enabling the comparison of delivered doses of drug in a specified time period and for specific drug formulations. Several protocols have been developed to evaluate nebulizer performance (Table 1). The various techniques consist of in vitro bench measurements, in vivo models, a combination of those 2 methods, and in vivo deposition and pharmacokinetic measurements. Though extremely useful and important tools for measuring and comparing performance of nebulizer delivery systems, the latter 2 methods are not reviewed here. All these methods can be applied to standard jet and ultrasonic nebulizers as well as to the newer breath-actuated and breath-enhanced designs.

Table 2 shows 4 types of in vitro tests for measuring nebulizer characteristics. They consist of methods for assessing variability in manufacturing of nebulizer plastic components, temperature change in the reservoir solution during nebulization, and drug available for inhalation when

Table 1. Assessing Nebulizer Performance: Protocols

In Vitro Models
- Filter collection of drug output (standing cloud) + particle size measurement
- Simulation of breathing patterns + filter collection of drug + particle size measurement
In Vitro/In Vivo Models
- Patient inhalation with filter collection of aerosol + particle size measurements
In Vivo Deposition/Pharmacokinetics
- Animal studies
- Human Studies

Table 2. In Vitro Tests of Nebulizer Performance

1. Variability in manufacturing between units
2. Temperature change in reservoir solution during nebulization
3. Drug output (solution; solvent/suspension) under continuous use and simulated/actual breathing patterns
4. Particle size characteristics under continuous use and simulated/actual breathing patterns

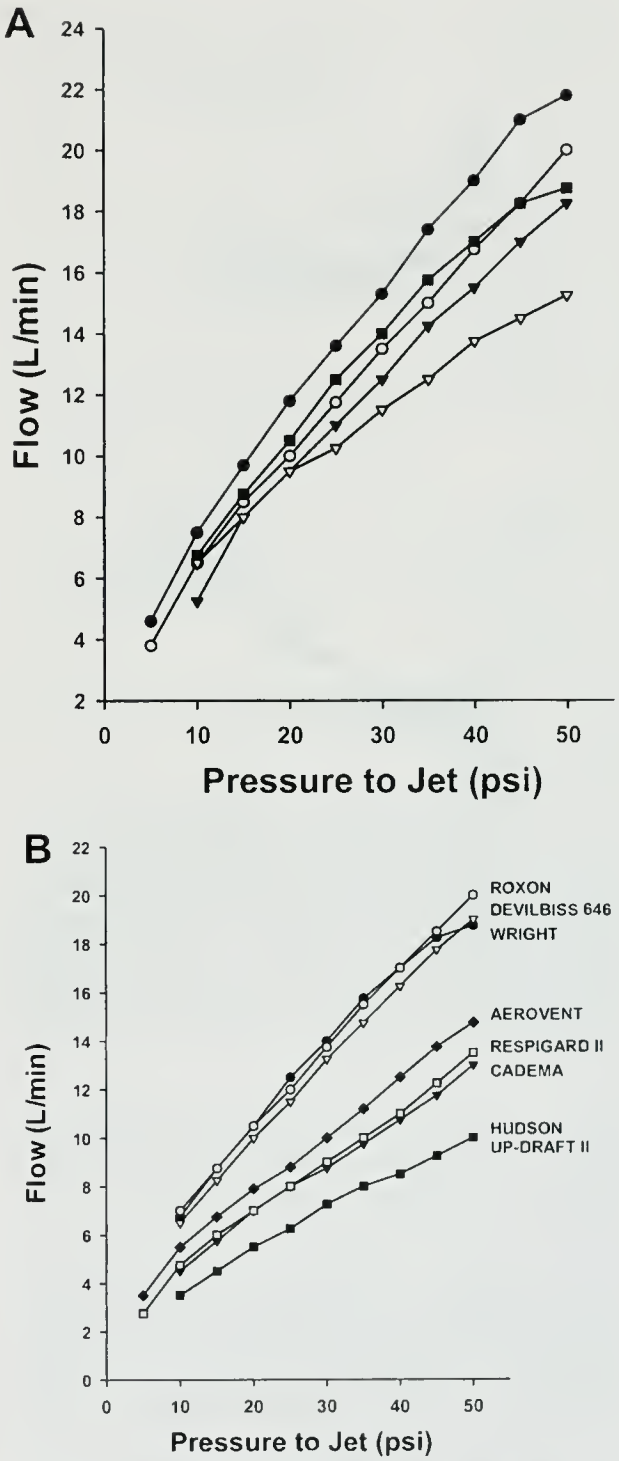

Fig. 1. A. Pressure-flow curves obtained with 5 Wright nebulizers, reflecting the variability in manufacturing between different units of the same type of nebulizer. The measurement is made without fluid in the nebulizer. The differences in air flow at the nebulizer exit, with a constant pressure applied to the jet, would give rise to differences in aerosol output between these nebulizers. B: Similar measurements for 7 different standard jet nebulizers, showing the variability between nebulizers.

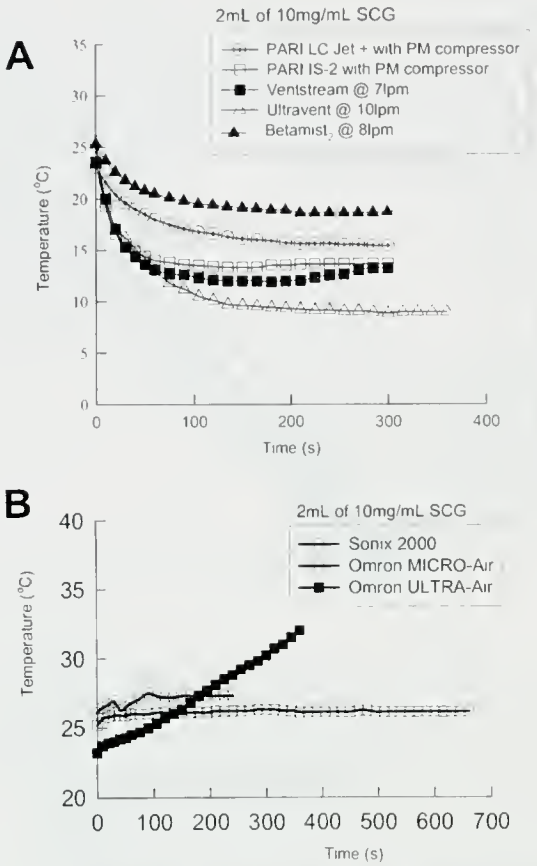

Fig. 2. A. Changes in jet nebulizer reservoir fluid temperature during operation. B. Similar measurements for several ultrasonic nebulizers. Temperature of the fluid dropped consistently for all the jet nebulizers during the initial 2 min of operation, whereas expected temperature increases were seen with only 1 of the 3 ultrasonic nebulizers tested. SCG = sodium cromoglycate. (Adapted from Reference 10.)

used in a continuous mode, in comparison to drug available with simulated breathing patterns. Measuring the particle size characteristics under these various conditions allows an estimate of the dose of nebulized drug potentially reaching the peripheral lung. Though testing performance on the bench is necessary for product quality control, information as to actual performance with patients is limited to selected populations. A more accurate assessment can be obtained by incorporating into in vitro test protocols actual conditions under which the nebulizer would

Table 3. In Vitro Drug Output Measurements

Drug output measured over time as:
1. Absolute drug content in aerosol over time
2. Change in weight and change in drug concentration of reservoir solution
3. Gravimetric (estimated) output: change in weight × nominal concentration

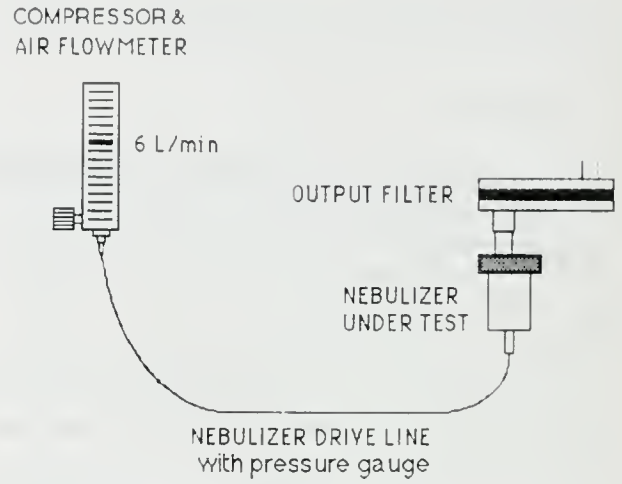

Fig. 3. Experimental set-up for collecting aerosol generated from a nebulizer by mounting an absolute filter at the nebulizer exit. (From Reference 11, with permission.)

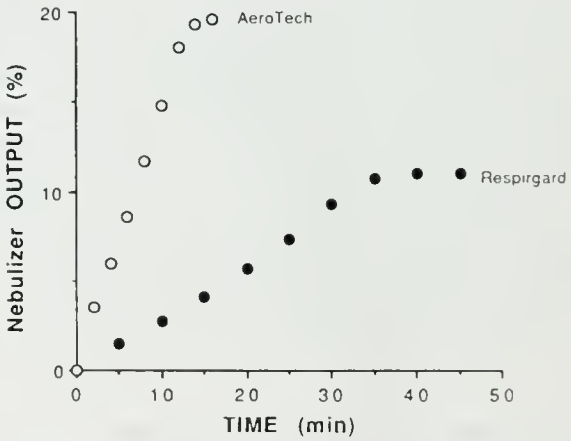

Fig. 4. Nebulizer output versus time. The 2 nebulizers shown have an approximately 4-fold difference in rate of aerosol output. (From Reference 12, with permission.)

Fig. 5. The Unit Dose Collection Apparatus (UDA) for aerosol emitted from an aerosol delivery device. The set-up is shown with a pressurized metered-dose inhaler interface, but similar connecting pieces have been made in our laboratory for nebulizers. The sample is collected in the tube and solvent added to absorb the drug on the filter. (From Reference 14, with permission.)

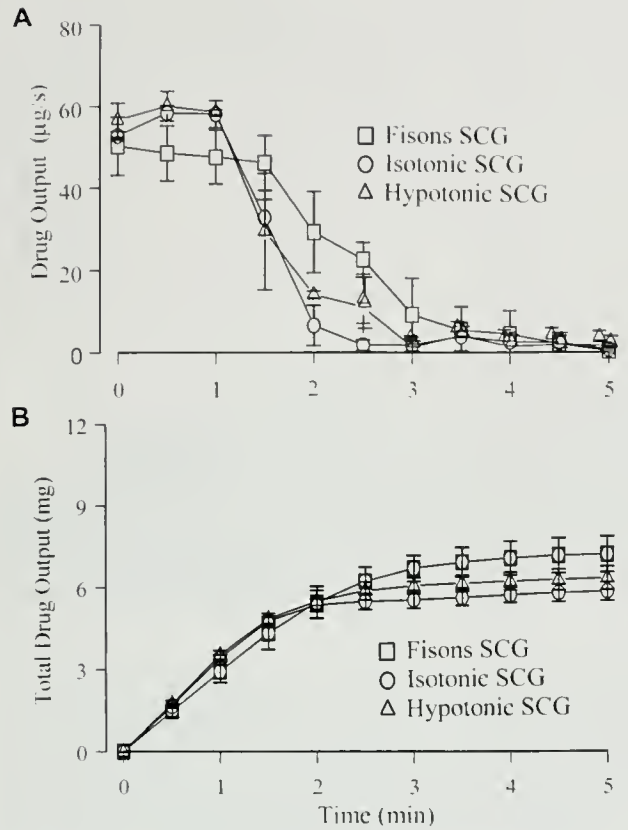

Fig. 6. A. Sodium cromoglycate (SCG) output per second from the Pari LC jet nebulizer, sampled every 30 seconds over a 5-minute operating period (reservoir fill: 2 mL of 10 mg/mL). A: In this example the rate of output is relatively constant for the first minute and then tapers off to zero over the remaining 4 minutes. B. Data replotted as cumulative dose of cromolyn available over the 5 minutes of operation. The rates of output for the 3 formulations of SCG were not markedly different. (Adapted from Reference 15.)

Table 4. Methods: In Vitro Drug Output

1. Absolute drug content in aerosol over time
   - -Nebulizer run continuously for 5 min
   - -Aerosol samples collected into a unit dose collection apparatus (UDA)*
   - -Aerosol samples collected for 10 s every 30 s
   - -Drug output determined by chemical analysis
   - -Drug output rate calculated by dividing amount of drug in UDA by collection period (10 s), and plotted vs time
   - -Total drug output calculated from area-under-the-curve
2. Change in weight (W) and change in initial drug concentration ($[\ ]_{initial}$) in reservoir solution: $\Delta W_t \times \Delta[\ ]_t$, where t = time
   - -Weight and concentration of reservoir solution measured before and after a nebulization period ranging from 30 s to 5 min with test nebulizer
   - -Drug output determined by: Output = $W_{initial} \times [\ ]_{initial} - W_t \times [\ ]_t$
3. Gravimetric (estimated) output: $\Delta W \times$ nominal concentration ($[\ ]_{nominal}$)
   - -ΔW_{5min} = weight change over the 5-min nebulization period measured for the nebulizer
   - -Drug output determined by: $Output_{5min} = (W_{5min} - W_{initial}) \times [\ ]_{nominal}$

*Per Reference 14

Table 5. Comparison of In Vitro Output Measurements*

Measurement	Cromolyn Output
UDA (aerosol)	7.20 ± 0.66 mg
$\Delta W \times \Delta[\ ]$ (solution)	7.90 ± 0.75 mg
Estimated (solution)	10.07 ± 0.47 mg†
Ratio of Measured to Estimated	0.78 ± 0.06

*Data were collected using a Pari LC Jet+ with a reservoir fill of 2 mL of 10 mg/mL cromolyn solution
UDA = unit-dose collection apparatus
ΔW = change in weight
$\Delta[\ ]$ = change in concentration
†Estimated value = $\Delta W \cdot \Delta[\ ]$ = UDA ($p < 0.05$)
(Adapted from Reference 17.)

be used. Clinical trials of a nebulizer product and specific drug formulation are necessary to demonstrate efficacy in patients, but are not reviewed here.

Testing for Variability in Manufacturing Between Units

A quick test that can be done on the bench to assess reproducibility between nebulizers is to measure air flow through the dry nebulizer resulting from an increasing pressure drop across the nebulizer jet orifice.[6] The volumetric flow of air at the nebulizer exit for units of the same nebulizer should be similar for a fixed, applied pressure (Fig 1A). This measurement of the volumetric flow of air or oxygen when there is no fluid in the nebulizer gives an indication of the resistance of the nebulizer, which is a function of its design. Making this measurement between nebulizers of the same type allows an assessment of the variability of the manufacturing and can also be used as an indication of reproducibility in output with use over time.[7] These are important issues when using a specific nebulizer for a clinical diagnostic test where the output (aerosol dose inhaled) needs to be the same between laboratories using the same type of nebulizer or when multiple units are used in the same facility for the same diagnostic test. The pressure-flow measurement can be used to compare different nebulizer systems (see Fig 1B)[8] and also provides a starting point for determining the pressure drop needed to be applied across the jet orifice to obtain equivalent outputs for the various nebulizers tested.

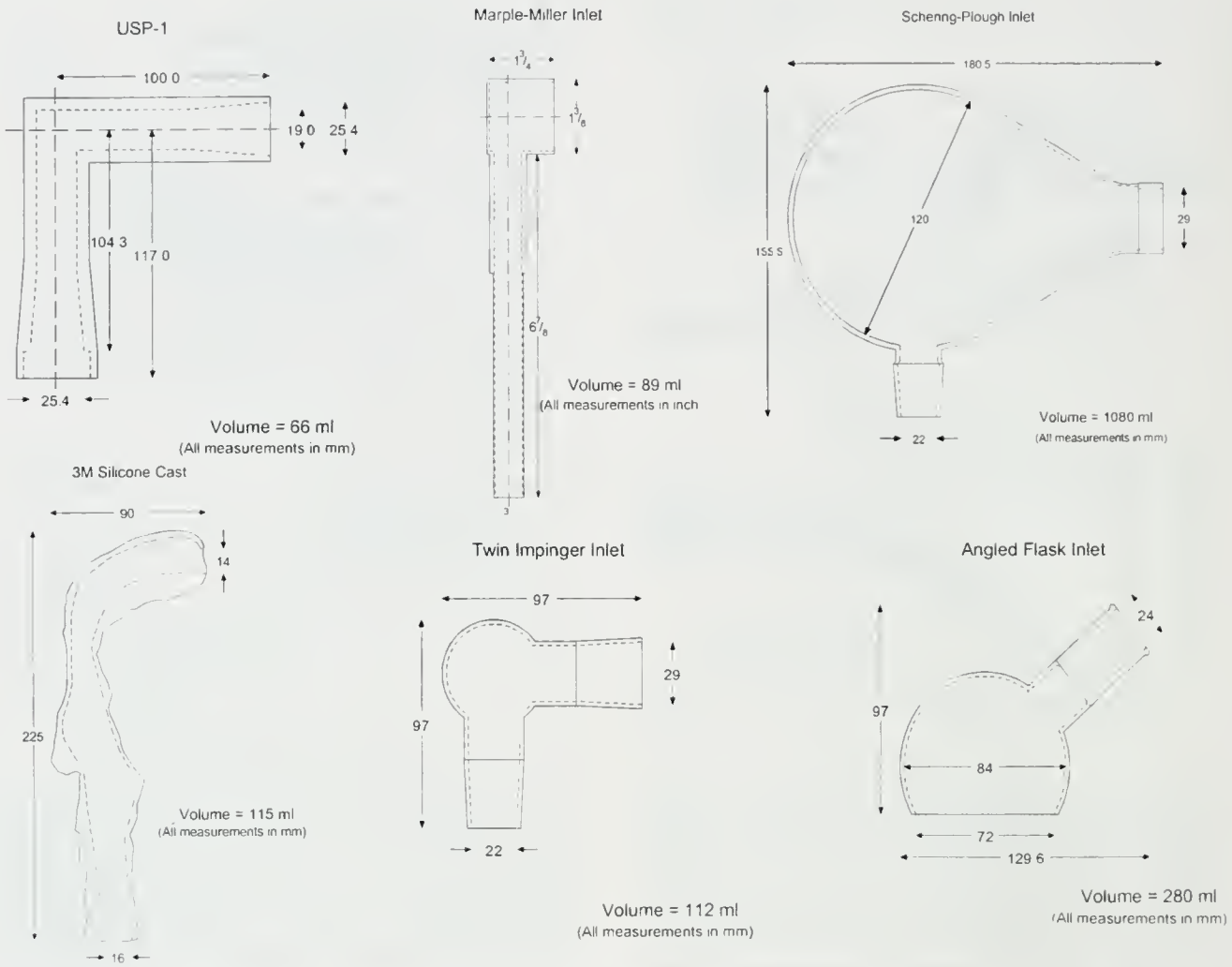

Fig. 7. Inlets used to couple a cascade impactor to an aerosol delivery system. The inlets range in volume from 66 mL to 1,080 mL. (From Reference 20, with permission.)

Temperature Change in the Reservoir Solution During Nebulization

During jet nebulizer operation, solvent evaporation decreases the reservoir solution temperature and increases the drug concentration in the reservoir solution and in the aerosol droplets.[9] Figure 2 illustrates the temperature change over 5–6 minutes of operation for 5 types of jet nebulizer and 3 types of ultrasonic nebulizer.[10] The figure shows a typical 12 °C temperature decrease with the jet nebulizers, but the temperature change differs among nebulizer designs and also varies with fill volume. Most of the temperature drop occurs in the first 60–90 seconds of operation, with the rate of temperature change decreasing slightly until nebulization stops. The temperature decrease can be described by the equation:

$$\text{Temperature (°C)} = A \times e^{(-kt)} + \text{Residual} \qquad (1)$$

in which A is a constant equivalent to the absolute change in temperature, k is a constant related to the rate of temperature change (the larger the value of k the more rapid the temperature change), and residual temperature is the temperature at the end of 5 minutes of nebulization. These terms are specific to each nebulizer.

In contrast to jet nebulizers, reservoir temperature can increase during operation with some ultrasonic nebulizers. This temperature increase was seen with the Omron Ultra-Air nebulizer (see Fig. 2B) but not with the Sonix 2000 or Omron MicroAir. The Omron Ultra-Air showed a roughly linear temperature increase, described by the equation:

$$\text{Temperature (°C)} = m \times \text{Time} + T_{initial} \qquad (2)$$

in which m is the slope of the line (in degrees Celsius/min), and $T_{initial}$ is the initial solution temperature.

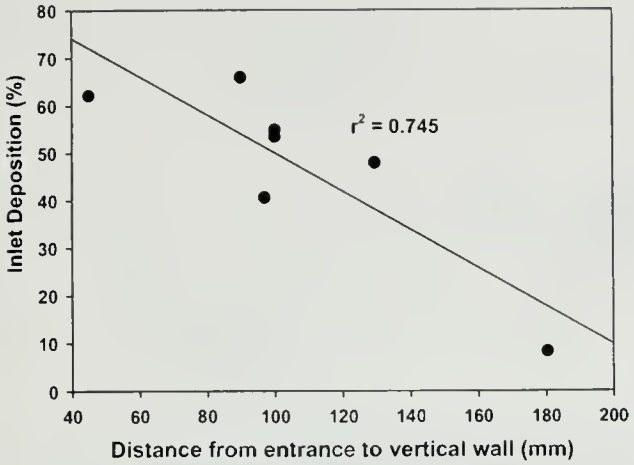

Fig. 8. Horizontal distance from inlet entrance to inlet back wall versus deposition of drug in inlet. The amount of aerosol deposited in the inlet is inversely proportional to the distance to the inlet back wall. Thus the greater this distance, the more aerosol is available for sampling by the impactor. (Adapted from Reference 20.)

With an ultrasonic nebulizer, if the formulation might be affected by increased temperature, the reservoir fluid temperature should be measured during nebulization, using a miniature thermistor threaded through the nebulizer out-port and into the fluid reservoir.

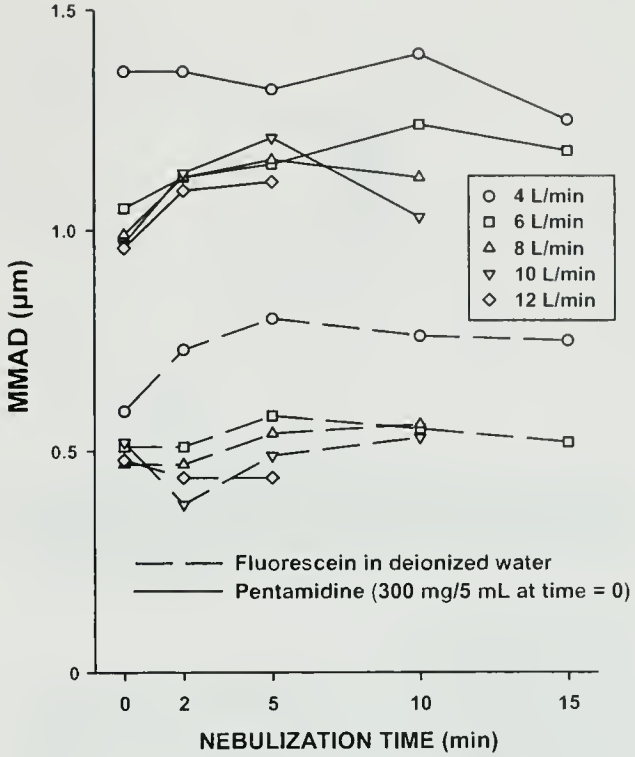

Fig. 10. Changes in particle size (mass median aerodynamic diameter [MMAD]) of pentamidine (60 mg/mL in 3 mL distilled water) over 15 min of nebulization. Changes were observed only during the first 2 minutes of operation. Drug added to the nebulizer (solid lines) increased the MMAD compared to the distilled water carrier alone (dashed lines). (Adapted from Reference 22.)

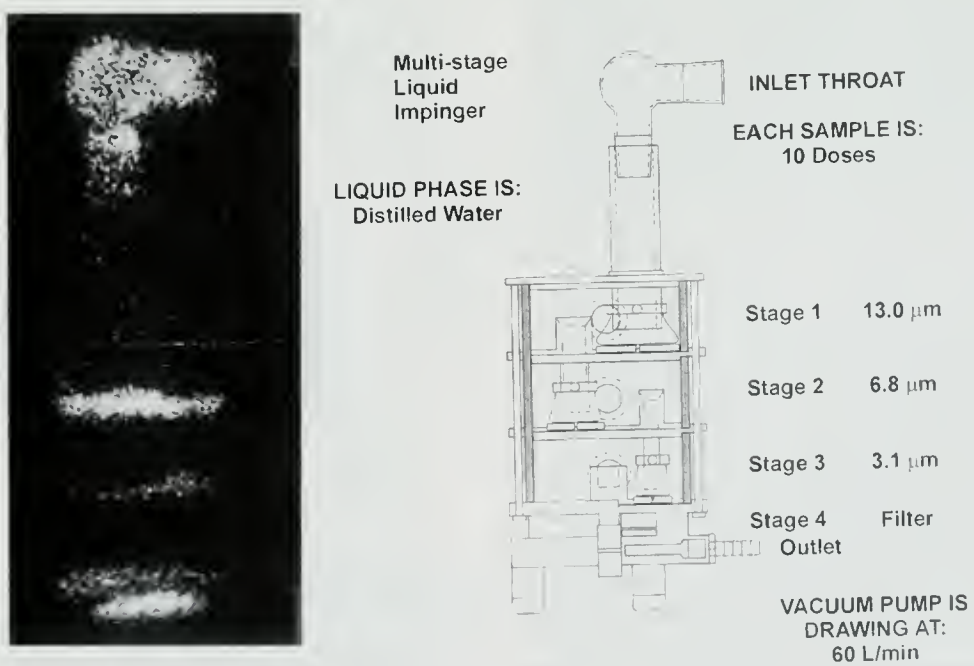

Fig. 9. Left: Gamma camera picture of a multi-stage liquid impinger (MSLI) following sizing of a drug solution containing a radiotracer. Right: Schematic of the MSLI with TI Glass Inlet and showing the stage cut-off diameters and the operating air flow rate. (Adapted from Reference 21.)

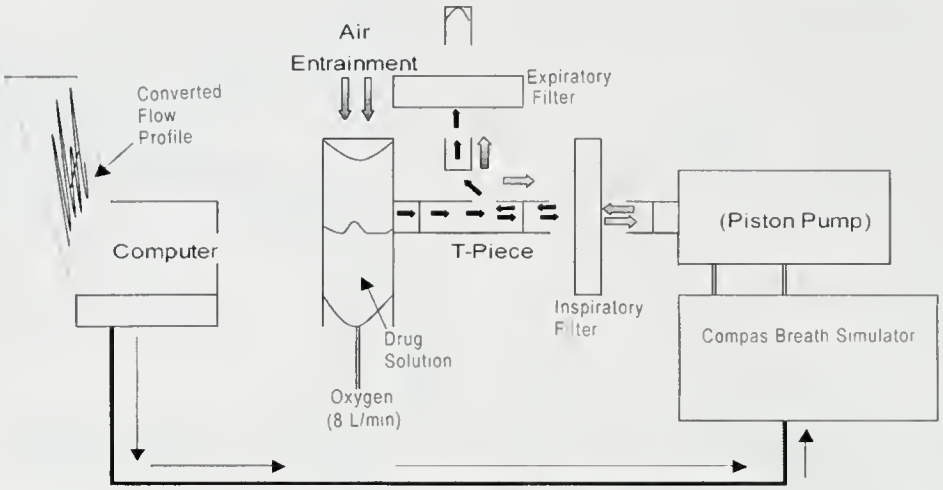

Fig. 11. Breath simulator set-up to measure nebulizer output with a fixed breathing pattern generated by the simulator, or alternatively, a recorded flow profile that is converted to a pattern file that is read and reproduced by the Compas Breath Simulator. Black arrows = aerosol flow. Shaded arrows = air flow. (Adapted from Reference 23.)

Nebulizer Output

There are a number of ways to measure how much aerosolized drug a nebulizer can deliver to the mouth for inhalation (Table 3). One of the simplest is the "standing cloud" method, in which the aerosol is collected with an absolute filter positioned at the nebulizer exit (Fig. 3).[11] The drug on the filter can be analyzed chemically, or if a radiotracer is also used, the activity on the filter can be counted in a γ counter. Aerosol can be collected at various points in time (Fig. 4). In Figure 4 the inhaled mass available increases with time, and there is also a marked difference in delivery between the nebulizers tested.[12]

The unit dose collection apparatus (UDA) described in Pharm Forum[13] can also be used to collect aerosol released from a nebulizer. In our laboratory, using the apparatus shown in Figure 5,[14] we collect 10-second aerosol aliquots every 30 seconds to obtain data of the sort shown in Figure 6A.[15] This type of measurement gives a rate of output in micrograms of drug per minute versus time of operation. The figure shows that the output rate is relatively constant for the first minute, tapering off until no aerosol is produced at about 6 minutes. The data can be re-plotted as a cumulative graph that shows the total drug output available over time (see Fig. 6B). The information in Figure 6B parallels that in Figure 6A, showing that, for that nebulizer, aerosol production increases at a constant rate for about the first 90 seconds. Total output gradually decreases with a decrease in aerosol generated. It can be seen why continuing nebulization past the knee of the curve, at about 80% of the maximum output, may not be advantageous for the patient in terms of added drug delivered.[16] Clinical measurements would need to confirm that response is only marginally enhanced by inhaling drug until aerosol production ceases.

Two other methods for assessing nebulizer drug output measure changes in the drug concentration and weight of the reservoir fluid. A gravimetric method based on weight changes applied to only the nominal concentration has also been used to estimate output. Table 4 shows the calculations used for these measurements of nebulizer output. We have compared output measurements for the Pari LC Jet Plus using the 3 methods in Table 4 and sodium cromolyn as a test solution.[17] The data in Table 5 show that assessing output by collecting aerosol aliquots to dryness using the UDA was not significantly different from weight and concentration changes occurring in the nebulizer solution. How-

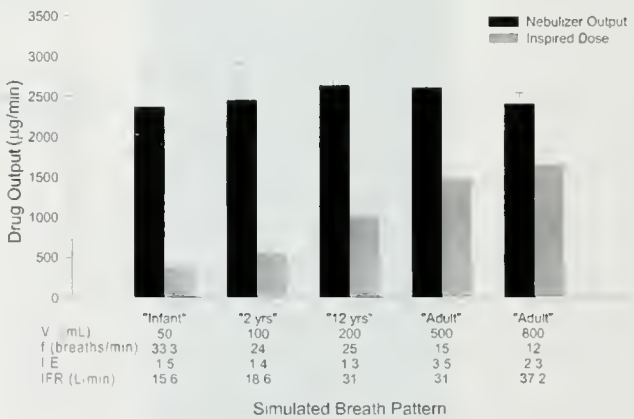

Fig. 12. In vitro measurement of the dose of cromolyn sodium available with the Pari LC Star nebulizer, for infant, child, and adult breathing patterns. The amount of drug delivered to a filter per minute of nebulization time increases with tidal volume and inspiratory flow rate, approaching the per minute output of the nebulizer when driven continuously, but only for the adult breathing pattern. V_T = tidal volume. f = breathing frequency. I:E = inspiratory:expiratory ratio. IFR = inspiratory flow rate.

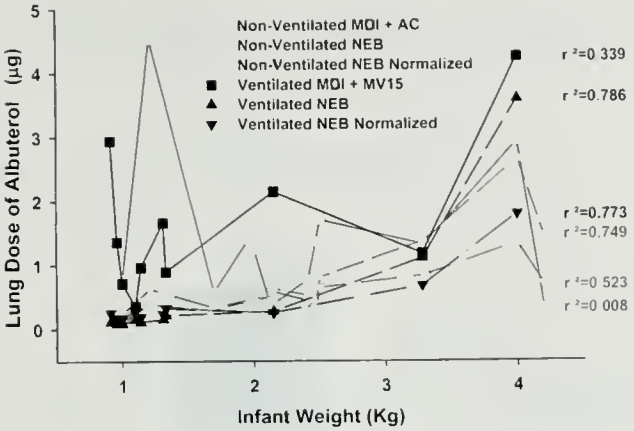

Fig. 13. In vivo lung deposition of radiolabeled albuterol in neonates with bronchopulmonary dysplasia versus infant weight. Delivery via the nebulizer but not the metered-dose inhaler increased with increased weight for both spontaneously breathing infants and intubated infants. MDI = metered-dose inhaler. AC = Aerochamber. NEB = nebulizer. MV15 = Aerochamber MV15. (Adapted from Reference 24.)

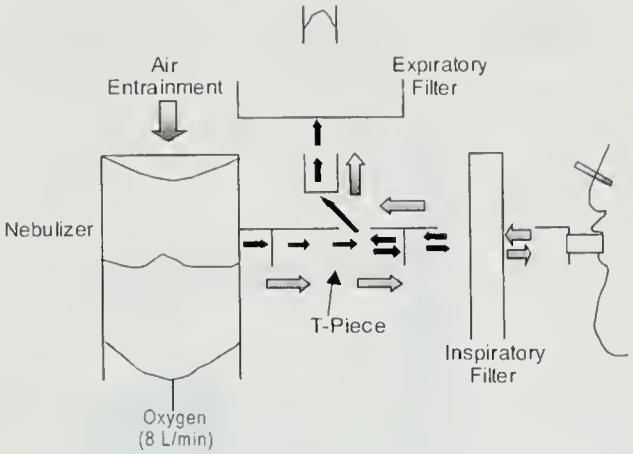

Fig. 15. Schematic of set-up to measure aerosol dose inhaled at the mouth. Subject breathes from the nebulizer and drug (levalbuterol solution: 1.25 mg/3 mL) is collected on an absolute filter between the mouth and the nebulizer. Black arrows = aerosol flow. Shaded arrows = air flow.

ever, estimating the output based on weight change alone and using only the nominal or starting concentration, rather than correcting for concentration changes within the same time period, overestimates drug output. Weight changes reflect not only solute (drug) loss but also solvent (saline or water) losses and need to be corrected for the parallel increased concentration of drug occurring in the nebulizer fluid.

Particle Size of the Nebulized Aerosol

Measuring the particle size of the aerosol exiting the nebulizer allows an estimate of the likelihood of the aerosol depositing in the lung and the site of lung deposition. The particle size data and the measurement of emitted dose are used to approximate the fine particle dose (dose carried by the percentage of particles < 4.7 μm) of the (emitted) aerosol, which is most likely to be delivered to the distal lung.[18] Cascade impactors and multi-stage liquid impingers are routinely used to determine the particle sizes of nebulizer-generated aerosols, both suspensions and solutions, providing data on the drug content of the various particle size fractions. Droplet size, which partly determines the site of lung deposition, is best measured by light-scattering devices such as the Malvern Mastersizer and Sympatec Rodos System, but these laser diffraction methods do not measure the amount of drug carried by the droplets. Typically, the median particle size reading from diffraction measurements is 1–2 μm greater than that from impactor measurements, primarily due to evaporation of

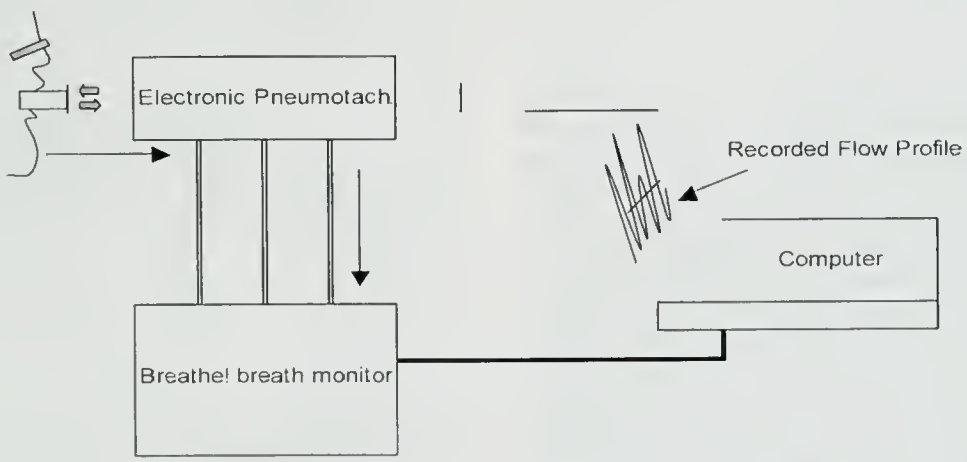

Fig. 14. Tidal breathing into the pneumotachograph connected to the breath monitor. Subject's breathing pattern is recorded on the computer for later use with the breath simulator. (Adapted from Reference 23.)

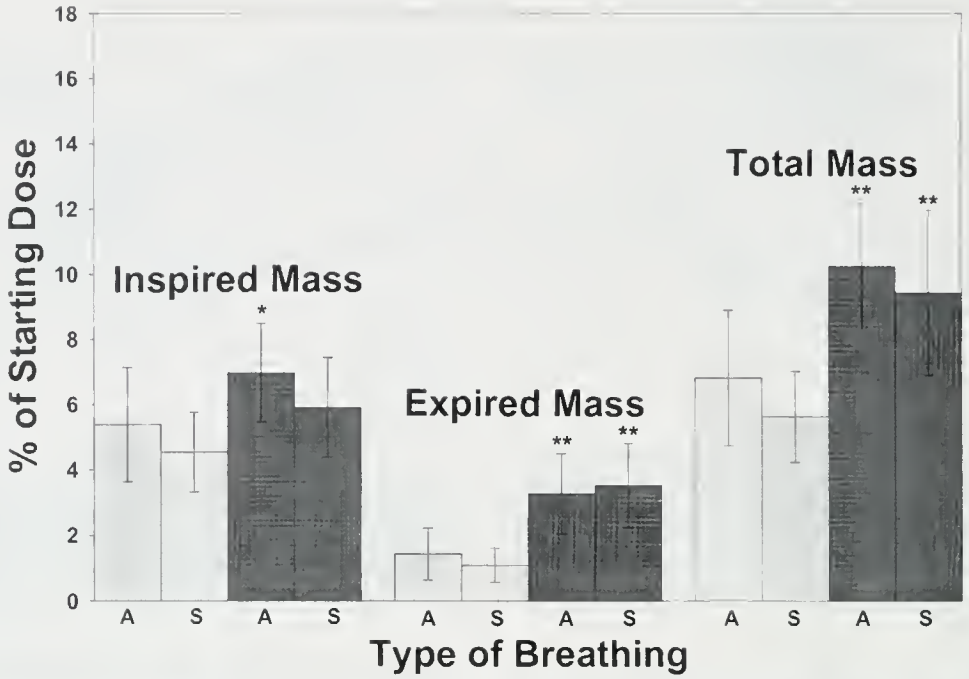

Fig. 16. Inspired mass, expired mass, and total mass of levalbuterol collected from the AeroEclipse (shaded bars) and the LC Star (black bars) during 1 minute of simulated breathing (type of breathing S) and actual subject breathing (type of breathing A). * $p < 0.04$ versus AeroEclipse actual breathing. ** $p < 0.01$ versus AeroEclipse actual and simulated breathing. (Adapted from Reference 26.)

solvent through the impactor. Ideally, an impactor should be used with an operating flow that matches that of the nebulizer. An alternative approach is to use a low-flow (< 1 L/min) impactor, inserted into the nebulizer circuit close to the mouth.[19] If the impactor is placed perpendicular to the flow of air, it samples only a fraction of the aerosol inhaled. However, isokinetic conditions need to be established so the air stream is not perturbed.

Another consideration when sizing aerosols is the inlet used to connect the nebulizer and the impactor. Figure 7 shows 6 types of inlet for impactor and impinger sizing systems.[20] The amount of aerosol that deposits in the inlet depends on the distance between the inlet's entrance and its back wall. Greater aerosol deposition in the inlet means less aerosol reaches the impactor (Fig. 8). Sampling times with nebulizer aerosols must be short to avoid fluid overload on the impactor stages. Fluid collected on the stages can be analyzed chemically. Adding fluorescein or radioactivity to the drug solution or suspension provides a second tracer for quantifying particle size. This may be particularly useful when testing suspension aerosols. Figure 9 shows a γ camera image of a multi-stage liquid impinger following sizing with a radiolabeled suspension[21] and shows the distribution of radioactivity in the inlet and the various stages. Attenuation factors for the various impinger stages (in particular the end-stage) must be factored into the determination of the dose per stage. Measurements demonstrating changes in particle size with nebulization time have shown that these changes occur mainly in the first 2 minutes of nebulization (Fig. 10), reflecting the change in reservoir fluid temperature.[22] In this example, the mass median aerodynamic diameter marginally decreases with increasing jet gas flow. In addition, the particle size of the carrier (which in Fig. 10 is fluorescein in distilled water), is significantly lower than for the drug dissolved in distilled water. Despite the concentration increase during nebulization, there is little overall effect on the aerosol particle size. Applying standard methodology

Table 6. Comparison of In Vitro Studies With the AeroEclipse Breath-Actuated Small-Volume Nebulizer

	Bosco et al[23,26]	Geller et al[27]	Archer et al[28]
	Levalbuterol (1.25 mg/3 mL)	Albuterol (2.5 mg/3 mL)	Albuterol (5 mg/mL)
IM (% start dose)	30.7 ± 5.1	30.8 ± 2.8	—
FPM (% start dose)	20.2 ± 3.3	22 ± 0.9	—
MMAD (μm)	2.9 ± 0.1	3.3 ± 0.2	3.0 ± 0.1
FPF (emitted % < 4.7 μm)	66 ± 4	68 ± 3	—
FPF (impacted % < 4.7 μm)	79 ± 3	—	82 ± 2

Values are mean ± SD
IM = inspired mass
FPM = fine particle mass
MMAD = mass median aerodynamic diameter
FPF = fine particle fraction

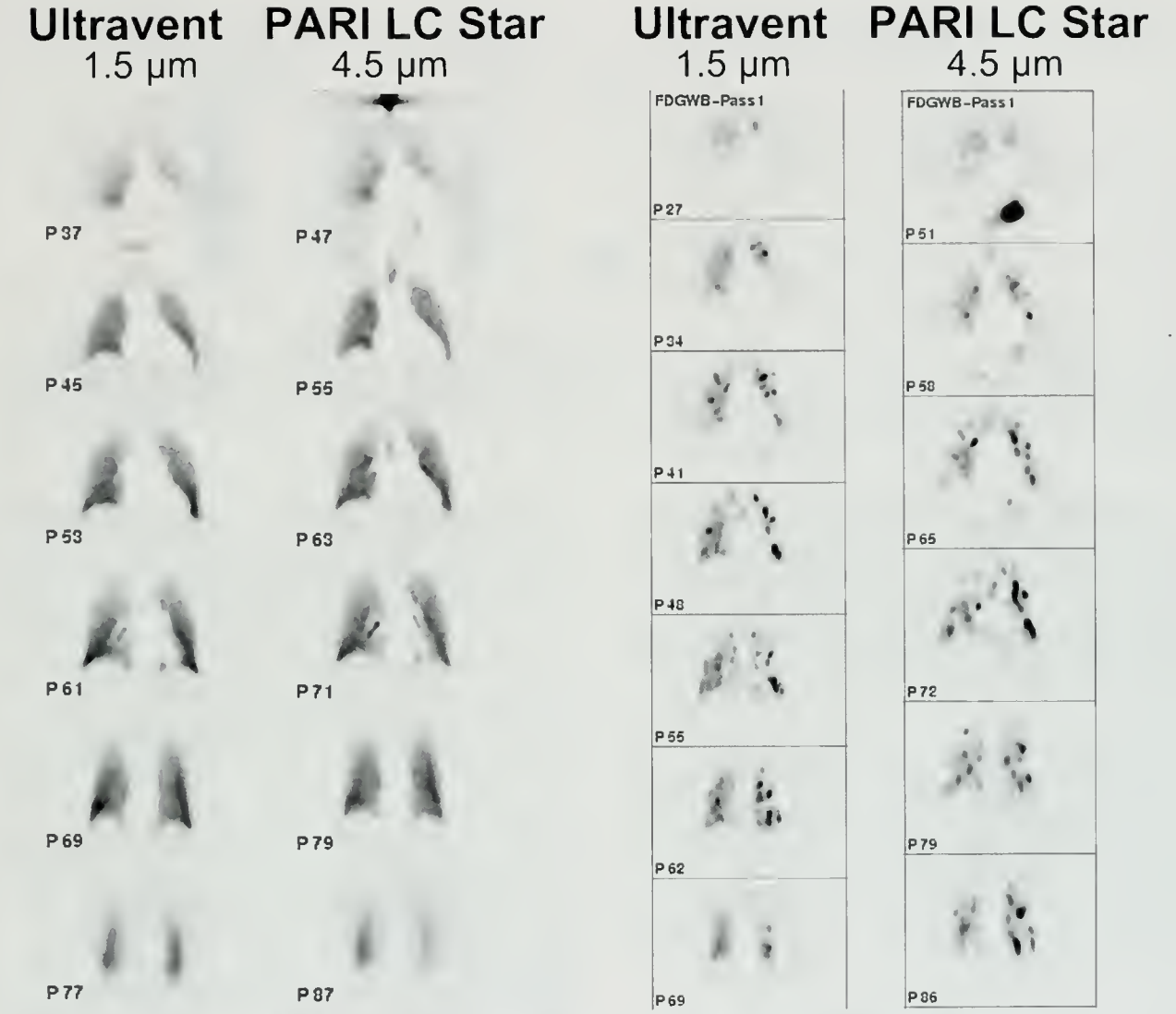

Fig. 17. In vivo lung deposition scans obtained via positron emission tomography following inhalation of a similar dose of tracer from 2 different jet nebulizers (Ultravent and Pari LC Star). Left 2 columns: Normal subjects. Right 2 columns (in boxes): Cystic fibrosis patients. Though marked differences are seen between the normals and the cystic fibrosis patients, only small differences are seen between the scans from the 2 aerosols. (Adapted from Reference 29.)

to the sizing data, the fine particle fraction (percentage of particles < 4.7 µm) can be obtained from the cumulative size distribution curve and applied to the measurement of emitted dose to give the fine particle dose available for inhalation at the mouth.[18]

Measuring Drug Output Under Simulated or Actual Breathing Conditions

Breath simulators can be used to drive nebulizers with standard breathing patterns (Fig. 11), providing measurements of aerosol delivery under breathing conditions that mimic actual adult and pediatric breathing patterns.[23] Figure 12 shows that, whereas the in vitro measurement of output per minute of cromolyn sodium from the Pari LC Star jet nebulizer is relatively constant during continuous operation, the actual drug inhaled at the mouth is a function of tidal volume and inspiratory flow. These in vitro measurements, obtained with the Compas Breath Simulator, show varying amounts of drug available at the "mouth" at the different settings. As tidal volume is a function of age, it can be seen in Figure 12 that younger children probably will not receive the same dose of aerosol from a nebulizer as an older child or adult, unless breathing time is prolonged. We have performed a deposition study in intubated and spontaneously breathing neonates with bronchopulmonary dysplasia, in which we compared lung delivery from jet nebulizer versus metered-dose inhaler (MDI)

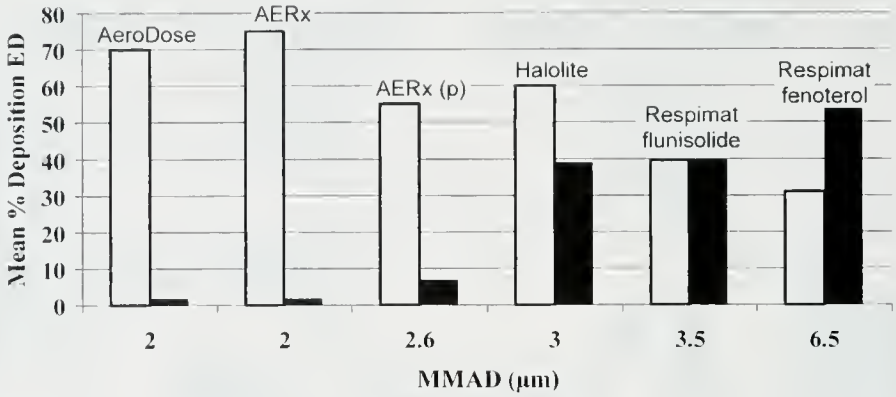

Fig. 18. Relationship between particle size (mass median aerodynamic diameter [MMAD]) and lung deposition (clear bars) and oropharyngeal deposition (black bars) for the new nebulizers. Efficiency of lung delivery is much higher than with conventional jet nebulizers. ED = emitted dose. (From Reference 18, with permission.)

with holding chamber.[24] Similar to the in vitro simulation experiments, we found a linear relationship between body weight (proportional to tidal volume) and drug deposition for the neonates breathing from the nebulizer (Fig. 13) but not with the MDI. However, the combination of a more concentrated aerosol from the holding chamber and shorter inhalation time resulted in a similar mean lung dose to these neonates.

Simulators can also be used to drive nebulizers with actual breathing patterns collected from human subjects. The breathing pattern is measured with a pneumotachograph and recorded by a breath-monitor/computer system (Figure 14).[23] The digitized breathing pattern is then used to control a breath simulator for nebulizer testing. Nebulized drug is collected on filters in the inspiratory and expiratory paths (see Fig. 11). We have used the simulation approach to compare aerosolized drug delivered to the mouth, using the same subjects actually breathing through the nebulizer but having the inhaled and exhaled aerosol collected on absolute filters placed between the mouth and the nebulizer exit (Fig. 15).[23,25,26] Though dependent on simulator function and inherent limitations of reproducing breathing patterns, we obtained a good correlation between the in vitro simulation and the in vitro/in vivo measurement of delivery of levalbuterol using both the AeroEclipse breath-actuated jet nebulizer and the Pari LC Star breath-enhanced jet nebulizer (Fig. 16). Furthermore, the amount of inhaled drug as a percentage of the reservoir fill as well as the particle size distribution data from our experiments confirmed measurements for the AeroEclipse from other laboratories[23,26–28] using similar experimental setups but different drugs (Table 6), which supports the advantage of duplicate measurements using standardized methodologies.

Table 7. Considerations When Selecting a Nebulizer

Clinical benefit
Ease of use
-Assembly, cleaning, portability
-Face mask vs mouthpiece
Rate of drug delivery
-Treatment time, dose in single actuation vs nebulization over time, frequency of treatments
Cost and convenience
-Cost of competing nebulizers
-Use with all drugs
-Replacement parts, accessories
Dose delivered
-Dose depends on inspiratory flow rate
-Breathing pattern required for optimal dosing
-Breath-actuated, synchronization with actuation (metered-dose liquid inhalers)
Aerosol characteristics
-Mass median aerodynamic diameter
-Fine particle fraction
-Fine particle mass
Upper and lower respiratory tract deposition
-Efficiency vs other aerosol systems
-Adverse effects

In Vivo Testing

When possible, in vivo testing of nebulizer performance should be done to provide actual use data to the clinician. In vivo testing usually consists of deposition measurements and/or clinical response data. Figure 17 shows in vivo positron emission tomograms of lung deposition in normals and cystic fibrosis patients.[29] Two types of nebulizer were used, with a 3-fold difference in median particle size between them. In theory, the finer aerosol should deposit more distally in the lung, but in the cystic fibrosis patients airway obstruction precludes that peripheral deposition. This type of information would not be obtained from the in vitro measurements described above. Figure 18 shows deposition data for some of the new-technology nebulizers discussed at the 30th RESPIRATORY CARE Journal conference on Liquid Nebulization: Emerging Technologies.[18,30] Lung deposition is much greater

with these new technologies than with the typical jet and ultrasonic nebulizers commonly used today. If these new nebulizers are used with the standard therapies (bronchodilators, inhaled corticosteroids, anti-allergics), adjustments to the nominal dose or inhalation time would be required to avoid adverse effects.

Summary

In vitro dose output and particle size measurements are necessary to assess nebulizer performance. In general, deposition data from in vitro studies tend to overestimate in vivo deposition data, in part because the dose to the oropharynx is not differentiated from the total drug captured on the filter. A complete assessment of nebulizer performance for a given drug would require in vitro measurements as discussed above, as well as deposition data in the target population and clinical response data. As outlined in Table 7, other practical information, such as ease of use, cost, and convenience for the patient, can be obtained, to judge how the tested nebulizer compares to other nebulizers and to other types of aerosol delivery systems.

ACKNOWLEDGMENTS

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Discussion

Smaldone: I enjoyed your talk, Myrna. I'd like to comment about our approach to these studies, because in some ways I agree with you and in other ways I don't. First of all, I'm not surprised that bench studies overestimate lung deposition, because they don't measure lung deposition; they measure the amount of drug that's presented to the patient, and with tidal breathing experiments (particularly in normals) the lung deposition is going to be less, because the aerosol gets exhaled. The advantage of bench studies is in comparing devices. You fix a lot of variables, you compare the devices, and then when you go into the clinical arena, you have some idea what your device *should* do under certain circumstances. I think that's the major advance, and it takes out the device difference; if you measure deposition in vivo but you don't measure differences between devices, then you have no idea why the deposition is different. I think that is the message to the clinician.

With regard to standards, I think there probably should be some standards, but they should be viewed for what they are, meaning recognizing that a USP [United States Pharmacopeia] throat is a USP throat, and when you measure a delivery using a USP throat, you have delivery with a USP throat. It doesn't necessarily say that one device is better than another, and it doesn't necessarily have any relevance to drug delivery in humans. There's always this overlap between whether you're predicting what's going to happen in the patient versus other reasons for doing a bench study, which is to compare devices, not to predict deposition. And I think standards are interesting and useful, but they can be constraining with regard to how you use the system. It has to be viewed very carefully, and it is going to be important to discuss this over the course of this conference.

Geller: I think it's important to do breath simulation experiments in a lot of cases with nebulizers, because the performance characteristics are different if you're using a T-piece versus a breath-enhanced versus a Sidestream nebulizer, for example. If you don't do breath simulation you only characterize how much aerosol is presented to the patient, but not how much they would inhale. Breathing patterns can significantly affect the amount of drug inhaled from different nebulizer types. So these kinds of issues are important, and looking at those data without breath simulation with different kinds of devices may not be optimal. In measuring particle size with a cascade impactor, how important is the effect of the cooling of the reservoir solution? Some of the new devices don't cause cooling.

Dolovich: I would think that if it's cooled there would be little change in particle size. The concentration of drug in the nebulizer is due to evaporation of solvent, and the rate of evaporation is a function of the temperature gradient between the solution and the air into which the aerosol is released. The maximum change in temperature occurs in the first 2 minutes, and we saw small changes in droplet size during that time, as measured with an Anderson cascade impactor.[1] After 2 minutes particle size changed minimally. If the nebulizer solution is cooled from the beginning of nebulization, I would expect little change in the particle size over the whole nebulization time. Presumably if the temperature of the air flowing through the impactor increases, then further evaporation of the aerosol would occur and an even smaller particle size would be measured.

The other issue is shearing when you're giving liposome formulations via jet nebulization. Is the repetitive cycling through the jet nebulizer going to cause degradation of a liposome formulation? It does in some cases. We have some data showing that shearing is an issue for liposomes aerosolized by some devices.

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Barry: Warren Finlay published some data in the *Journal of Aerosol Medicine* that showed that the Anderson cascade impactor warms up as you use it, and that that changes the measured particle size.[1] He placed an Anderson impactor in a water bath and kept it at a constant temperature and got different results. We presented some data at the Aerosol Society's "Drug Delivery to the Lungs" meeting[2] that showed that the liquid impinger cools down as you use it, because of latent heat of evaporation, and that changes the emitted particle size. So there are issues with that.

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Dolovich: I know that these changes have been documented and that the changes measured are small. When you take those changes, calculate the difference in micrograms of drug delivered to the mouth, and then add the patient's clinical status on top of that, are we really looking at major clinical effects resulting from those changes during nebulization? I think not. But, having said that, it is important to understand the process.

Smaldone: I think every situation depends on what you're looking at and what you want to talk about. We've been concerned about the issue of tem-

perature changes and recently we looked prospectively at temperature changes.[1] It is indeed true that nebulization cools the nebulizer, but by the time the particles get to the mouthpiece—and we've measured temperatures in various types of systems—they're very close to room temperature. So it depends on what you want to look at; with low-flow cascade impaction we've cooled down cascade impactors and gotten data similar to what Stapleton reported,[2] but it primarily affects the geometric standard distribution of the particles, not the mass median aerodynamic diameter. Our observations, for whatever kind of experiments, do not indicate that one system is better than another.

When you're measuring something, it depends on what you want to measure. Stapleton used an Anderson cascade impactor that runs at 28 L/min, which I would never use in a nebulizer circuit. I have no idea how that would relate to anything that we would do in a closed nebulizer system. But for a metered-dose inhaler it makes a lot of sense. In our experiments, by the time the particles get to the mouthpiece they're close to room temperature.

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Barry: This raises the issue of comparing studies between laboratories. You need to state the exact methods of an experiment, and if you don't control those, then it is not just *devices* that you are comparing, but also the way you and I do experiments.

Smaldone: These issues apply to any other engineering problem in any engineering laboratory. If you state the conditions under which you do your experiments, then you can make comparisons. If it was important to compare differences, say, between our lab and yours, if the conditions are stated then you should be able to reproduce and comment on those differences, as we did with Stapleton's experiments. We did our experiments under a different set of conditions; we got a different set of results, which have relevance to each scenario. But I'm not going to say that our technique is better than Stapleton's.

Fink:* One of the keys to this seems to be educating the clinician or end-user about how to interpret these studies, and to understand how these variables in the experimental model affect the results so that they can compare and apply them in a meaningful way. It's a daunting task. Is it reasonable to take a bench model with some in vivo correlation and develop a database so that you have predictive capability from in vitro data to in vivo?

Dolovich: I think it is. But I would use a simulator with actual breathing patterns recorded from patients rather than setting it up to test an ideal breathing pattern, because that does make a difference. If you can capture patient breathing patterns and feed them into the simulator, I think you'd be 2 steps ahead of just setting up the simulator to drive the nebulizer under ideal conditions.

MacIntyre: I want to echo Jim's [Fink] point. I think clinicians get confused because they don't understand what the numerators and denominators are when we talk about deposition fractions. Sometimes the denominator is the amount we start with in the nebulizer, sometimes it's what comes out of the device, and sometimes it's what goes into the mouth. The numerator gets confusing too. Are we talking about what's in the airway? What's in the lung? What's in the thorax as a whole? I just find it very confusing when we talk about "deposition" and express it as a percentage when we haven't clearly defined what the numerators and the denominators are. My question is, what about this measuring of urine or serum concentrations as the ultimate reflection of deposition? You didn't mention that as an in vivo test.

Dolovich: No, I didn't, but urine and plasma levels have certainly been used as a measure of deposition in a number of studies. An early study from Michael Silverman measured sodium cromoglycate in urine from babies, and the delivery was $< 1.5\%$.[1] These measures don't tell you *where* the drug is; they only tell you what's been absorbed from the lung and into the circulation and excreted. You can't determine *regional* distribution of drug with those urine or serum measurements. It tells you something about delivery, but not the whole story.

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Rau: I think that's an important problem you've addressed. I teach students and *we* need to know what to teach them, and that's what they want to know: what is the correct thing? What does this do? Which way should we do it? One solution would be that every lab does everything exactly the same; that's not likely and not practical, because we do what we can and sometimes we're looking at different things. But I do think it links to the regulatory issue. It is nice, though, to have *some* data that are comparable, and that is done under some form of standardized conditions. This was the case with the USP standards for testing plumes from metered-dose inhalers. At least if you have that, then you can go changing other things, looking at other breathing patterns, with sim-

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ulators, and so forth, that academicians can play with to see "what happens if." But it is nice to have some common denominator somewhere, and I think that gets to the regulatory issue, not the research issue that many of us are involved in.

Dolovich: I can't agree with you more. I think the regulatory requirements are for a different purpose. They need to have you show what the device produces compared to a device already on the market, and whether there's going to be a benefit to the patient from that particular device. But that doesn't take into account all the other questions.

Dhand: One of the factors that you alluded to, and we have to consider it as an important factor, is the disease itself. As you showed, there was a significant difference between cystic fibrosis patients and normals. I'm sure that those differences translate into differences in patient response. Thus, not only are the age, lung size, and airway geometry important; the presence of airflow obstruction is also important. For example, in terms of bronchodilators, the site of the air flow obstruction and absolute lung size are important variables that influence how much deposition occurs and where.

The second point I want to make is about the plasma measurements that Neil [MacIntyre] brought up. Using the urine is a simpler estimation because there's much more drug in the urine than there is in the plasma. But there are more confounding factors when you analyze drugs in urine than in plasma. So we like to analyze the plasma rather than the urine to determine how much drug is absorbed from the lung. If you look at the first 30–60 minutes after inhalation, especially with albuterol, you get a fairly clear picture of what's coming through the lung, because the gastrointestinal absorption takes a little longer, and you see that peak somewhere between 60 and 120 minutes after inhalation. So if we restrict ourselves to the 30–60 minutes after inhalation, we can get a fairly good, although indirect, estimate of how much drug deposition is occurring in the lung.

Smaldone: Regarding Joe's [Rau] comments about teaching and regulation, I agree that there has to be standardization for comparisons, and, again, using the MDI scenario, in my opinion the regulatory aspect of bench testing for MDIs is QC [quality control], period! I think that's the way it ought to be for nebulizers, and if you want to do that with the simulator, that's fine with me. But then, to add on a statement that a given technique is universally "better for patients" or a better predictor of deposition or whatever, is a mistake, I think, because there are so many other issues involved, and then it becomes constraining. It then becomes a marketing issue. I think we have to stay away from that. If you want to have QC, that's fine, and I think that's important.

For example, right now there is no QC for the sale of 510(k) [section 510(k) of the Food, Drug, and Cosmetics Act] devices. The issue of reproducibility is important, and it ought to be standardized, but to imply that a fixed technique can determine that a device is better under all circumstances is very difficult to accept because of the vagaries of human physiology and disease. I'm all for testing—we do it all the time, and we use it all the time—but that's from a scientific point of view, not a QC point of view. And I think that if that makes teaching complicated, that's too bad. There's a certain amount of QC that you develop, and then there's all the rest of it. But I'm worried that we're going to regulate ourselves into a corner.

Dennis: We've been involved in standardizing nebulizer output in Europe for 2 decades, and I want to make one point. There are no clinical trials done for most nebulized drugs, whereas there are for MDIs. So physicians can rely on clinical evidence for MDIs and they can make valid decisions. When they come to choose a nebulizer delivery system, they can't interpret the stuff that's out on the marketplace. It's warped. Even if it's not warped, it's very difficult to interpret. Unless you have some level playing field somewhere, a valid decision can't be made by your average clinician in the field. That's why I think we need some kind of regulatory standard—some kind of consistent set of results that does not stop for the research, that doesn't stop for the testing and the desired experiments for particular applications. There has to be some leveling of the playing field.

O'Riordan: For nebulized drugs the FDA relies on clinical trials rather than bench studies. Ideally they want the drug matched with the nebulizer and the compressor for the clinical trial. That's the combination that should be marketed afterward. The FDA is reluctant to draw clinical implications from bench testing. I think that's a wise policy, because inhalation therapy can be "chaotic" in terms of aerosol generation and physiology and breathing pattern, making it difficult to extrapolate from existing bench techniques.

Formulations and Nebulizer Performance

Thomas G O'Riordan MD

Introduction
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  Solubility in Water
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  Hydrophobic Suspensions
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Summary

To deliver a drug by nebulization, the drug must first be dispersed in a liquid (usually aqueous) medium. After application of a dispersing force (either a jet of gas or ultrasonic waves), the drug particles are contained within the aerosol droplets, which are then inhaled. Some drugs readily dissolve in water, whereas others need a cosolvent such as ethanol or propylene glycol. Some drugs are delivered as suspensions, and the efficiency of nebulizers can be different for solutions and suspensions. Solutions are delivered more efficiently with most devices. In general, conventional ultrasonic nebulizers should not be used to aerosolize suspensions, because of low efficiency. Newer strategies to improve the delivery of non-water-soluble drugs include the use of liposomes and the milling of the drug into very small "nanoparticles." In addition to the active therapeutic ingredient and solvents, drug formulations may include buffers (the solubility of some medications is influenced by pH), stabilizers, and, in the case of multi-dose preparations, antibacterial agents. Though formulations are designed to optimize drug solubility and stability, changes in formulation can also affect inhaled mass, particle size, and treatment time, though the differences between nebulizer brands probably have a greater impact than differences in formulation. Ultrasonic and jet nebulizers may damage protein and other complex agents through heat or shear stress. Additives to multi-dose formulations, especially antimicrobial and chelating agents, may cause adverse events, so there is a trend towards single-use, preservative-free vials. *Key words: nebulization, nebulizer, aerosol, formulation, nanoparticles.* [Respir Care 2002;47(11):1305–1312]

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Introduction

Aerosolization of aqueous solutions and suspensions is an important therapeutic option in the management of respiratory disease. Even though the majority of patients with respiratory disorders use pressurized metered-dose inhalers and dry powder inhalers to administer inhaled β-agonists and inhaled corticosteroids, nebulization remains a popular choice for certain groups of patients: for example, corticosteroids are nebulized for young children, and β_2-agonists are nebulized for critically ill, emergency room patients. In those settings, nebulizers' simplicity of use and reliability are advantageous because patient cooperation may be limited.

Nebulizers are also an attractive option for drugs that need to be delivered in relatively large quantities (eg, hundreds of milligrams in the case of antibiotics for cystic fibrosis patients). In addition, because of the relatively simple design, nebulizers will probably remain an attractive option for early "proof of concept" studies with new chemical entities and the exploration of new indications for established medications. The latter objective has often been pursued by aerosolization of existing intravenous or even nasal formulations. However, the recent death of a research volunteer[1] after inhalation of an investigator-prepared formulation of hexamethonium is expected to lead to closer scrutiny of proposals for inhalation of new chemical entities or formulations that are only approved for noninhalation modes of delivery.

Solutions

To deliver a drug by nebulization the drug must first be dispersed in a liquid (usually aqueous) medium. Ideally the drug should be in solution, which is defined as a system in which soluble solid particles are dispersed in a liquid medium.[2-6] After application of a dispersing force (either a jet of gas or ultrasonic waves), the drug particles are contained within the aerosol droplets, which are then inhaled.

Solubility in Water

Solubility in water should be the first consideration in the development of a formulation for nebulization. Though not all medications are readily soluble, a number of strategies have been employed to increase aqueous solubility:[2-6]

1. Cosolvents. The aqueous solubility of some medications can be enhanced by the use of cosolvents. A cosolvent is a water-miscible agent in which the medication is freely soluble and has a dielectric constant similar to water. Ethanol and propylene glycol are used as solvents and are well tolerated in low concentrations. It should be remembered that all cosolvents and other excipients in therapeutic formulations have to undergo a toxicology evaluation that can be as rigorous as that required for the active ingredients of the formulation. For that reason, well-tested cosolvents such as propylene glycol and ethanol are preferred over novel compounds in drug development.

2. pH Adjustment. The solubility of weak acids and bases can be enhanced by pH adjustment.[2-6] In addition to their effect on solubility, pH adjustment and buffering are also important for the shelf-life stability of solutions and may be important for their effects on the airway. For example, the β_2-agonists albuterol and terbutaline are more stable in an acid pH. The pH of therapeutic agents is usually > 3.0. If the solution is buffered, there will be a greater impact on the pH of the airway, thus maintaining the drug at a favorable pH at the site of delivery. The considerable buffering capacity of the lung means that formulations with a pH > 3.0 are usually well tolerated, although a pH of > 5.0 may be preferable for subjects with airway hyperreactivity.[7]

3. Solubilization Agents (Surfactants). These are a third option to increase solubility. The agent should have a hydrophile:lipophile ratio of 15 and be miscible in water. Like cosolvents, they have been shown to be safe for inhalation.[2]

Nonaqueous Solutions

Though ethanol can be substituted for water, it tends to be irritating to the airway and is best used as a cosolvent in a more dilute form. Propylene glycol is less irritating but is also usually used in a dilute form. In high doses, propylene glycol can produce clinical features suggestive of mild ethylene glycol toxicity, but such findings have not occurred at the doses used in conventional pharmaceutical development. Formulations of cyclosporine that use ethanol and propylene glycol have produced therapeutic benefits in patients with advanced lung allograft rejection.[8,9] Though the propylene glycol was better tolerated than the ethanol, patients experienced cough and upper airway irritation with both formulations.

Modification of Other Characteristics of Solutions

Other characteristics of solutions that may affect their nebulization characteristics include surface tension, viscosity, density, tonicity, and volatility.[2,3,6-11] In pharmaceutical development these variables are changed when substances (either medications or excipients) are added to water, because most commercial inhalation formulations are aqueous. Changing these characteristics may affect the size of the aerosol droplets, the inhaled mass (the percentage of the nebulizer charge that is available for inhalation), or the time required for nebulization.

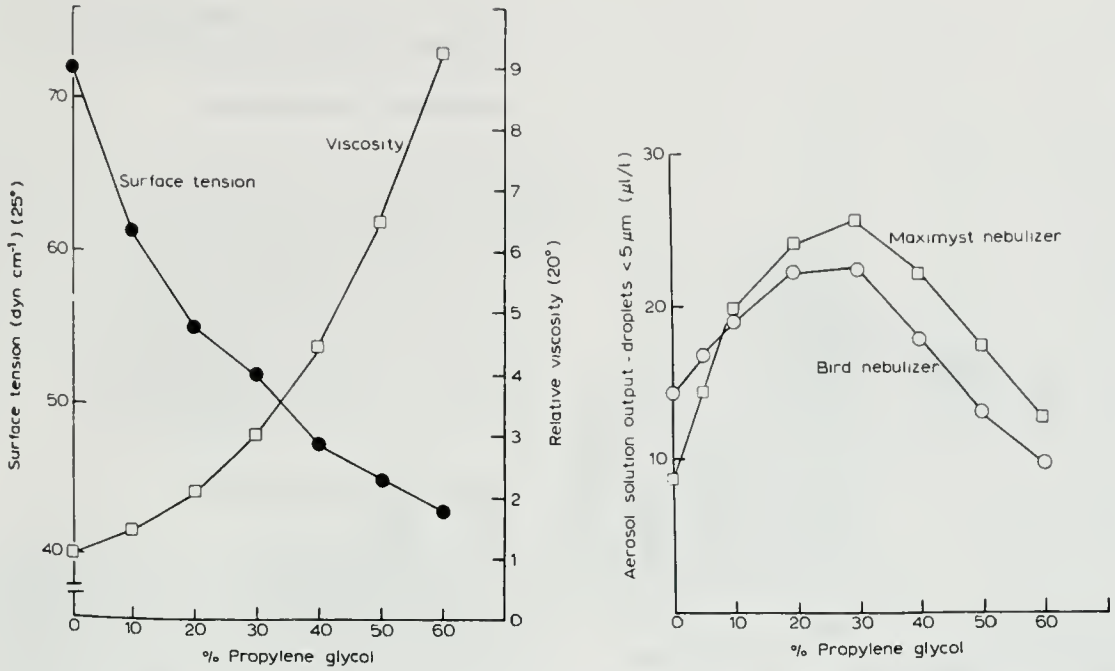

Fig. 1. Left: Effects of increasing concentrations of propylene glycol on surface tension (closed circles) and viscosity (open squares). Right: Effects of the change in propylene glycol on particle size, using 2 nebulizers. (From Reference 11, with permission.)

1. Modifying Surface Tension, Viscosity, and Density. Assessing the effects of changing one variable is complicated by the fact that changing one variable may also alter another variable (eg, decreasing surface tension by adding propylene glycol may increase viscosity) (Figure 1).[12] In general, it is believed, all other factors being constant, increasing surface tension, viscosity, or density results in larger aerosol droplets and increases inhaled mass.[10] However, though modifying those variables can affect the droplet size of the primary aerosol, the effect of nebulizer design, especially the design of baffles and methods of solution "recycling" within the device, are thought to be much more important determinants of the aerosol particle size.[5] For example, Newman et al studied the effects of different viscosities and surface tensions on the droplet size from commercial nebulizers and found no relationship between droplet size and those 2 variables. They did, however, observe that the increased viscosity of a carbenicillin solution was associated with longer treatment time.[12]

2. Volatility. Figure 2 shows an extreme example of how altering volatility can affect nebulizer performance. Though the inhaled mass of nebulized propylene glycol and ethanol are similar, the time needed to achieve the inhaled mass is 5 times longer with propylene glycol.[13] Volatile aerosols can be irritating to the airway, and the droplets in a dense aerosol cloud may be prone to coalesce into larger droplets.

3. Changes in Tonicity. Increases in tonicity can occur during nebulization if the solvent nebulizes faster than the solute, increasing the concentration in the nebulizer cup.[14,15] The tonicity increases in the nebulizer cup appear to correlate with increased concentrations in the aerosol droplets (Fig. 3). However, the changes differ among various formulations of the same medication. Concern has been expressed that the increased tonicity may cause bronchial irritation in children with airway hyperreactivity,[7] and because this phenomenon is time-dependent it has been pro-

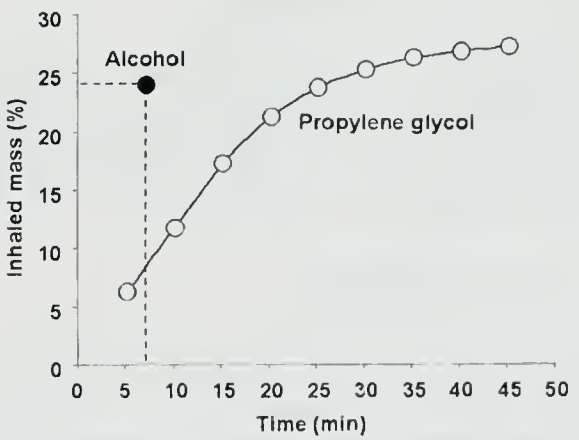

Fig. 2. Comparison of the inhaled mass and treatment time of a solution of propylene glycol (open circles) and ethanol (closed circle). Note the similarity in inhaled mass but the marked difference in treatment times. (From Reference 13, with permission.)

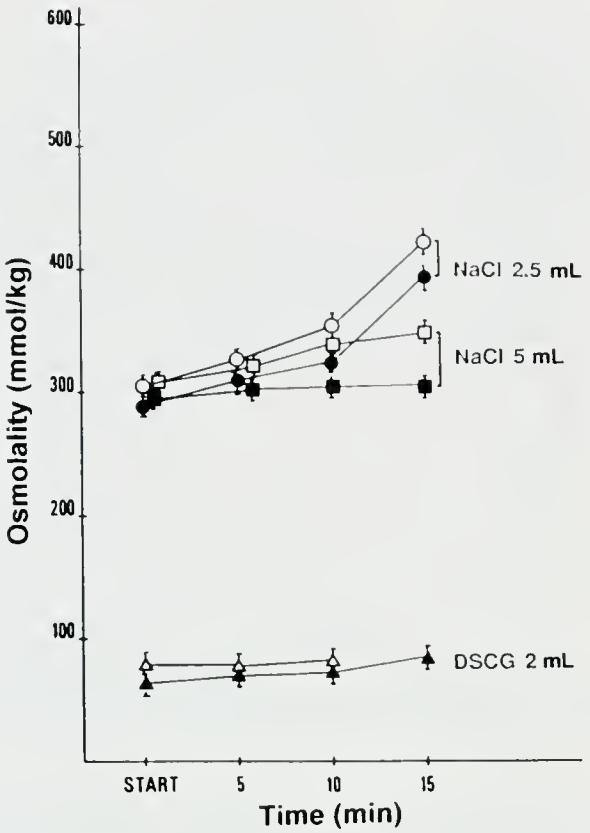

Fig. 3. Comparison of osmolality measured in the air stream (open circles) and in the nebulizer reservoir (closed circles), with 2 starting volumes of normal saline (NaCl), and with disodium cromoglycate (DSCG), with 2 nebulizers (Novair and Hospitak). (From Reference 15, with permission.)

posed that certain formulations be subject to a maximum nebulization time.[14]

Suspensions

A suspension is a system in which insoluble solid particles are dispersed in a liquid medium.[2,5] Most pharmaceutical suspensions are classified as coarse suspensions because the mean particle size is > 1 μm. The drug particles are generally manufactured by milling or crystallization.

Hydrophobic Suspensions.

The internal phase charaeteristics of a suspension can be classified as hydrophilic or hydrophobic.[2,6] With hydrophobic suspensions certain agents can be used to increase aqueous dispersion. Wetting agents (eg, surfactant in low concentration) are commonly used to reduce contact angle between particles and liquids. Hydrophilic colloids (eg, alginates) are rarely used in pharmaceutical formulations. Wetting with alcohol is another alternative. The use of liposomes is discussed below.

Deflocculated Suspensions

Suspensions can be flocculated or deflocculated.[2] Almost all pharmaceutical suspensions are deflocculated. In a deflocculated suspension, weak electrostatic bonds develop between the particles, which settle out of suspension in loose aggregates that are readily dispersed by shaking. In contrast, a flocculated suspension will settle on the bottom of the container, forming a cake that is difficult to disrupt for nebulization. Deflocculation is generally achieved by the addition of salts.

Nebulization of Suspensions

In general, suspensions are less efficiently nebulized than solutions (Fig. 4).[14,16,17] This is particularly true of conventional ultrasonic nebulizers. During ultrasonic nebulization the transmission of energy to the surface of the liquid causes droplet formation from the surface. Because of the tendency of the drug particles to settle beneath the surface, the aerosolized droplets may not contain drug particles. Similarly, a jet nebulizer that efficiently produces a 1–2 μm aerosol from a solution may be inefficient in nebulizing a suspension if the particles are too large to be entrained by the droplets. With nebulizers there are wide differences in the delivery efficiency of suspensions and solutions. It should not be assumed that an efficient nebulizer for solutions would be equally efficient for suspensions. Specific testing of the suspension should be undertaken with each device considered for use.

Nanosuspensions

Preliminary data (see Table 1) indicate that milling budesonide particles into submicronic nanoparticles increases the efficiency of budesonide delivery via conventional jet nebulizer, a conventional ultrasonic nebulizer, and a new aerosol device (Pari eFlow electronic inhaler) that uses a vibrating crystal to generate aerosol.[18] Nevertheless, the efficiency of the conventional ultrasonic nebulizer was significantly less than that of the other 2 devices, suggesting that even with nanosuspensions conventional ultrasonic nebulizers should not be used. Another preparation, which used nanocrystals of budesonide (particle sizes of 0.1–1.0 μm), delivered via jet nebulizer, also produced a higher proportion of respirable particles than a conventional budesonide suspension.[19]

Though nanosuspensions show promise of enhancing delivery, a safety concern may need to be addressed with regard to small particles. Inhaling small insoluble particles, especially particles < 0.05 μm, may have a tendency to provoke an inflammatory response in the lung.[20] The

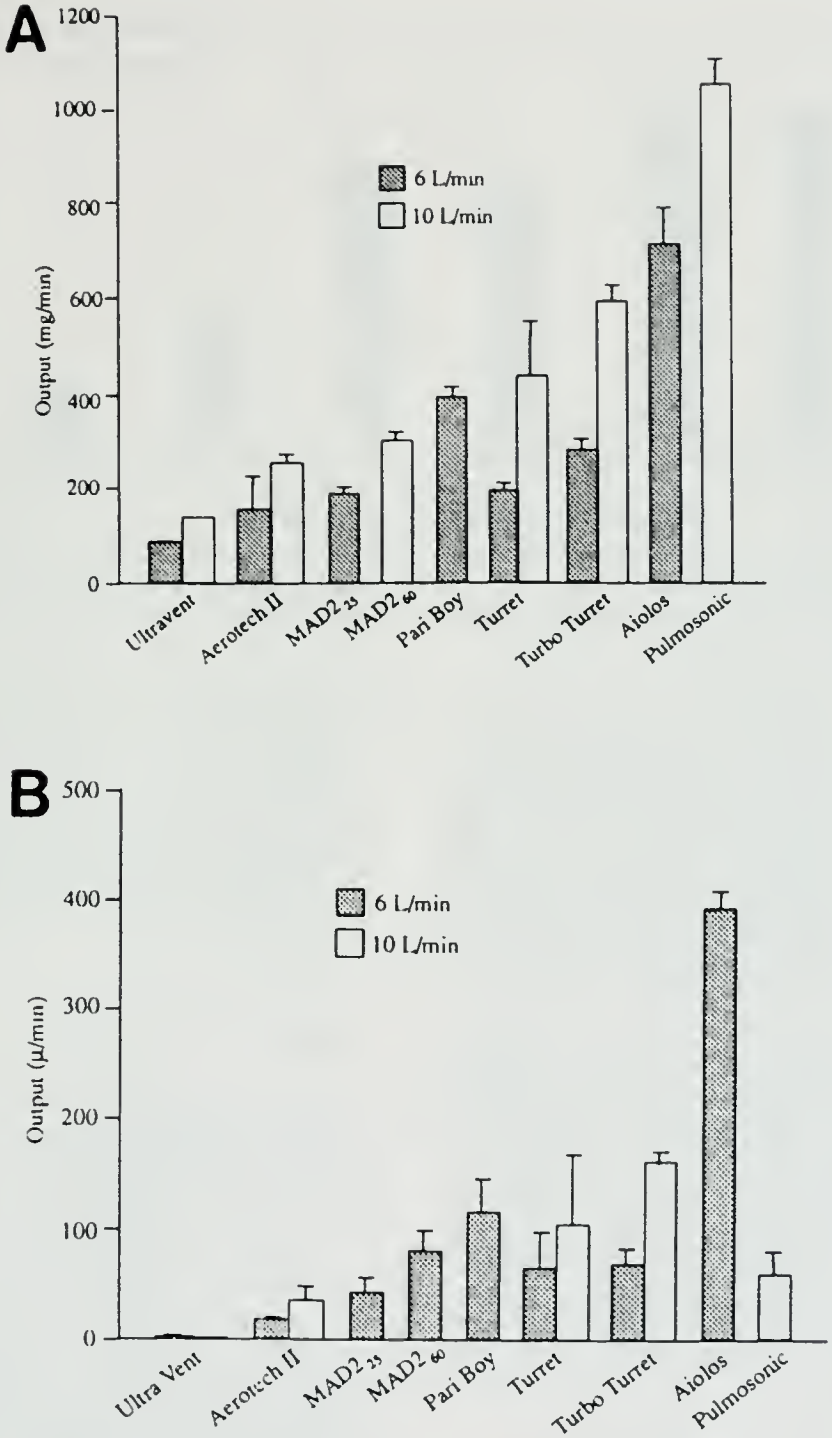

Fig. 4. Nebulizer outputs with a saline solution (A) versus a budesonide suspension (B). Note the marked performance difference with the ultrasonic device (Pulmosonic). (From Reference 16, with permission.)

nanoparticles described by Keller[18] were 0.8 μm in diameter, and those described by Mohsen et al[19] ranged from 0.1 μm to 1 μm, so this concern may not apply to these formulations. However, if particles are milled to smaller diameters, this concern would have to be addressed.

Liposomes

Liposomes can be defined as microscopic spherical vesicles that form when phospholipids are hydrated.[21,22] Liposomes offer an alternative approach to nebulizing non-

Table 1. Effect of Nebulization and Formulation Type on Aerosol Output Characteristics

Budesonide (1 mg/2 mL)	Emitted Aerosol Weight Loss (g)		Delivered Dose (μg)		Fine Particle Fraction (% < 5.8 μm)		Respirable Dose (μg)	
	Pulmicort	BSS	Pulmicort	BSS	Pulmicort	BSS	Pulmicort	BSS
Pari LC Plus	1.4 ± 0.1	1.5 ± 0.1	252 ± 9	386 ± 11	63 ± 3	70 ± 3	160 ± 6	269 ± 8
Multisonic Infra Control	1.1 ± 0.1	0.9 ± 0.1	47 ± 6	77 ± 5	75 ± 4	82 ± 3	35 ± 5	63 ± 4
Pari eFlow	1.6 ± 0.1	1.6 ± 0.1	246 ± 27	462 ± 27	92 ± 2	91 ± 2	227 ± 25	421 ± 41

BSS = balanced salt solution
(Adapted from Reference 18.)

water-soluble drugs. A bench study by Berlinski and Waldrep showed that a liposome (dilauroylphosphatidyl choline [DLPC]) formulation of budesonide resulted in greater inhaled mass than did a conventional suspension (Fig. 5).[22] DLPC has also been used to deliver cyclosporine in vitro and to animal models.[20]

It has been also shown that jet nebulization of a mixture of water and sheets of phospholipid can produce liposomes of respirable diameter,[21,22] indicating that the liposomes do not have to be preformed as spheres of appropriate size. In selecting the type of phospholipid for liposomes it is desirable to use a substance with a gel-to-liquid temperature that is above the operating temperature of the nebulizer; otherwise, the material may be too rigid for nebulization. It should be borne in mind that the solution temperature in a jet nebulizer may drop as much as 15° F or 10° C. Though that is not a concern for most drugs, it could a have a very important effect on certain liposomes.

The use of liposomes has also been advocated to prolong aerosol particle residence time in the lung and thus improve deposition, but the feasibility and utility of that property have not been convincingly demonstrated. Nebulized liposomes are being studied as vectors for gene therapy of lung disease.[23,24] Cationic liposomes, and more recently cationic polymers, have been complexed with deoxyribonucleic acid[24] and administered via inhalation, as an alternative to viral vectors. It has been reported that some of the formulations are more susceptible than others to time-dependent shear stress degradation during jet nebulization (Fig. 6).[24]

Preservatives and Antioxidants

The trend in the development of commercial formulations is that unit-dose formulations are replacing multi-dose formulations,[2,6] primarily because of the need for preservatives in multi-dose formulations. Antimicrobials such as benzalkonium have been reported to cause bronchospasm. Also, oxidation can decrease the activity of a medication. In a sealed unit-dose container, nitrogen can be used as an antioxidant, but that protection is lost once the vial is opened. For multi-dose preparations, chelating agents (eg, ethylenediaminetetraacetic acid [EDTA], citrate) prevent oxidation by binding the metallic ions that catalyze oxidation. However, chelating agents have also been implicated in bronchospasm. In contrast to multi-dose formulations, unit-dose preparations are often labeled as "preservative free" because they do not contain antimicrobials or antioxidants. Clinical adverse events associated with preservatives and other additives have been reviewed by Beasley et al.[7]

Another trend in the development of commercial nebulizer formulations in the United States has been for unit-dose vials to avoid the use of adhesive labels, relying instead on embossed lettering. This is because of concern that the adhesives used in the label may leech through the plastic vial and contaminate the formulation, albeit at very low concentrations.

Alterations to Formulations During Nebulization

Jet and ultrasonic nebulizers can alter medications through shear stress and heat stress, respectively.[3,6] Ultrasonic nebulizers generate heat during nebulization and the heat produced is proportional to the frequency. Higher frequencies produce smaller particles (most devices operate at 1–3 MHz; at 5 MHz water boils!). Thus, it is in the nebulizers that are designed to produce small particles that heat stress is most likely. Complex proteins and gene therapy vectors are much more liable to damage than are small molecules such as albuterol, which are generally unaffected. Various methods of conducting the heat away from the solution have been tried, with variable success.[4]

Jet nebulizer shear stress damage to proteins and gene therapy vectors may also occur.[24] Because increasing the nebulizer power-gas flow rate yields smaller particles, the small-particle nebulizers may be more likely to produce such stress, although factors other than flow also affect particle size, so that risk is not predictable. In contrast to ultrasonic nebulizers, the solution temperature decreases during jet nebulization, which could be a problem for some

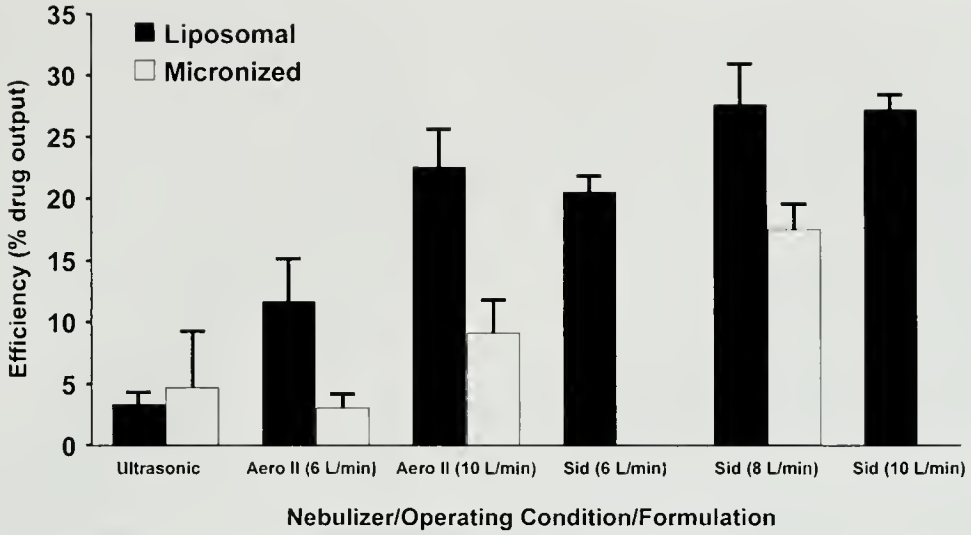

Fig. 5. Output efficiency (percent of drug output [measured with an Andersen cascade impactor] divided by nominal dose) in the 0.4–0.5 μm particle size range of budesonide (micronized and liposomal formulations) with various nebulizers and operating conditions. Values are mean ± SD of 4 samples. Aero II = AeroTech II nebulizer. Sid = Sidestream nebulizer. (From Reference 22, with permission.)

liposomes, the consistency of which is temperature-dependent. Evaporation may increase viscosity and tonicity (discussed above), and the concentration increase may decrease the solubility of antibiotics, thus necessitating greater volumes of diluent and causing longer treatment times, which may negatively impact patient adherence. In contrast to tonicity, pH remains unchanged during nebulization.[14]

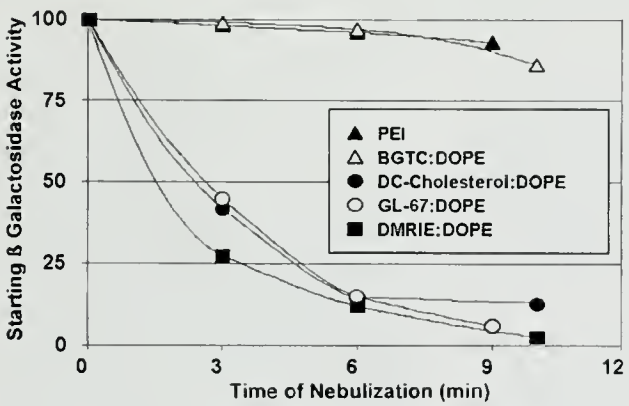

Fig. 6. Effect of jet nebulization time on the transfection ability (assessed as percentage of starting β galactosidase activity) of different formulations of gene therapy vectors. Two formulations, one based on cationic polymers (polyethyleneimine [PEI], closed triangles) and one based on a cationic liposome formulation (porcine cytomegalovirus [pCMV], open triangles), maintained most of their activity through 9 minutes of nebulization, but the other 3 formulations of cationic liposomes (closed and open circles and closed squares) had lost most of their transfection ability after 3 minutes, presumably succumbing to shear stress. DC = deoxycholic acid. DOPE = dioleoyl-phosphatidylethanolamine. DMRIE = 1,2-dimyristyloxypropyl-3-dimethylhydroxyethylammonium bromide. (From Reference 24, with permission.)

Summary

There are significant differences in nebulizer performance between suspensions and solutions. In general, conventional ultrasonic nebulizers should not be used to aerosolize suspensions. Though formulations are designed to optimize drug solubility and stability, changes in formulation can also affect inhaled mass, particle size, and treatment time. Nevertheless, it is likely that differences between nebulizer brands have a greater impact than differences in formulation. Liposomes can improve nebulizer delivery of agents that are poorly soluble in water. A theoretical advantage of liposomes is that they may improve particle residence time in the lung, but this remains unproven. Aerosolized liposomes are also being studied as vectors for gene therapy. Propylene glycol is an acceptable solvent for cyclosporine in lung transplant patients. Ultrasonic and jet nebulizers, especially those designed to produce small particles, may damage protein and other complex agents through heat or shear stress, respectively. Additives to multi-dose formulations, especially antimicrobials and chelating agents, may cause adverse events, so there is a trend toward using single-use vials.

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Discussion

MacIntyre: When does a particle become a nanoparticle? How small does it have to be?

O'Riordan: They are solid particles less than 1 micron in diameter. I think there are only 2 nanosuspensions available: one made by Pari and one by Sheffield Pharmaceuticals.

Dolovich: When you stressed the problems with ultrasonics, you were referring to the traditional designs, in which the piezoelectric crystal vibrates at a high frequency. What about the newer types of ultrasonics, designed around a vibrating mesh?

O'Riordan: The Pari eFlow nebulizer performs better with suspensions than do conventional ultrasonic nebulizers, but published data are limited. Regarding the whole issue of nebulizing suspensions I didn't see much data; a lot of the data are proprietary.

Dolovich: I think that at one of the RDD [Respiratory Drug Delivery] symposia, Sheffield Pharmaceuticals presented a poster about their ultrasonic device, but I don't remember the details. I am not familiar with their technology.

Smaldone: I would support the vibrating mesh idea, in general. We have done some testing. One company, Omron, has another form of vibrating mesh that also has proven effective at nebulizing suspensions of budesonide. I should point out, though, that there are some data indicating that particle size is affected by the vibrating mesh; in the Omron studies we did, even though that device was very efficient, the particles were somewhat larger than you'd get out of a jet nebulizer. So what's really happening with suspensions is that anything that can throw off the larger particles would be more efficient. There were some data at the RDD VIII meeting that showed that the eFlow mesh is less efficient with a budesonide suspension than it was with solutions, because their mesh prevented the large particles from going through.

Dolovich: You mentioned that budesonide liposomes continue to be less exact and that there doesn't seem to be an advantage in terms of long-term release in the lung. There is good literature about the inhaled liposomes of the antioxidant glutathione, that

show high levels of the drug in the lung up to 24 hours.

Fink:* You showed Keller's data that the Pari eFlow nebulizer demonstrated less efficiency with standard budesonide than with their nanosuspension budesonide formulation,[1] but their performance with standard budesonide was still better than the Pari LC with the same dose. Those data are consistent with our findings with the Aerogen technology, in which the vibrating aperture plate has similar characteristics to the e-Flow, in that there is a tendency to have a "sieve" effect with larger suspension particles. If the aperture diameter is 5 microns, particles bigger than that obviously aren't going to go through, so even though standard budesonide has a mean particle diameter of 2.5 microns, there will be some particles larger than 5 microns that will remain in the reservoir. Beyond that, we did not see a shift in particle size with the suspension, and I suspect from Keller's presentation at RDD VIII that they did not see a change either.

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Smaldone: The topic of liposomes is getting interesting. Is Waldrep's technique universal? It seems to me that some companies make their liposomes first, then put them in the nebulizer and hope that they don't get destroyed. Whereas Waldrep uses the nebulizer to "create" the liposomes. They throw a bunch of lipid in the nebulizer, then they throw in a bunch of drug, and it makes what they *say* are liposomes. Other companies make a liposome, put it in the nebulizer, and hope that it doesn't get destroyed. What's the difference?

O'Riordan: Liposomes change during jet nebulization. They seem to get smaller. There have been some studies showing that drugs do tend to leak out of the liposomes during nebulization.

Smaldone: So what they're doing is using liposomes as a solubilizing agent, and the other companies are using liposomes as expensive delivery systems that presumably will do something good in the lung.

O'Riordan: It is not known how long the drug remains bound to the liposome after deposition in the lung, and the effects on absorption are difficult to predict and cannot be generalized.

Dolovich: We nebulized cationic liposomes for gene therapy. Those liposomes take on a spaghetti-and-meatballs appearance when the plasmid is added to the lipid. The particles change from approximately 1 micron to form an elongated structure. Nevertheless, when you put these liposomes in the nebulizer, a certain percentage of them are sheared, so that you get free plasmid, lipid, and the intact liposome. The person inhaling the aerosol would be inhaling *free* drug, lipid, and liposomes together, so you don't know whether the clinical effect is coming from the free component or from the bound component.

Nebulizer Therapy for Children: The Device-Patient Interface

Bruce K Rubin MD MEngr FAARC

Introduction
Choice of Equipment
Aerosol Size and Airway Deposition
Special Medication Delivery Issues for Infants and Children
Airway Diameter and Particle Deposition
Patient Cooperation and Aerosol Delivery
Care of Nebulizer Equipment
Reasons for Nonadherance to Therapy
Summary

A therapeutic aerosol benefits the patient only if the medication deposits in the airway. Advances in nebulizer design have made them more efficient and "user friendly," but the greatest problem with administering aerosolized medication continues to be educating patients and caregivers to use aerosol devices properly and consistently. Misuse and nonuse are the greatest impediments to effective aerosol delivery. The respiratory pattern and degree of patient cooperation also profoundly affect aerosol deposition, and those effects are greatly magnified in small children. There are many misconceptions about nebulizer use and nebulizer equipment, even in teaching hospitals, and these can have serious consequences when patients do not receive the medication they need. This review discusses how airway physiology, nebulizer technology, and patient education relate to appropriate nebulizer use. Education is critically important, but unfortunately it is often a misunderstood or neglected part of aerosol administration. *Key words: aerosol therapy, children, pediatric, nebulization, asthma.* [Respir Care 2002;47(11):1314–1319]

Introduction

Choice of Equipment

Modern jet nebulizers were introduced in 1958, with the Wright nebulizer.[1] In the last few years, nebulizer technology has rapidly evolved, improving the efficiency and ease of use of many of these devices. For nebulizer *therapy* to work well, the *nebulizer* must work well, the *nebulizer-patient interface* must work well, and *patient* must understand proper technique. This review focuses on the nebulizer-patient interface and problems associated with nebulizer therapy in children.

Nebulizer performance varies with diluent volume, operating flow, pressures, gas density, and nebulizer model.[2–6] The residual volume of medicine that remains in commercial small-volume nebulizers ranges from 0.5 to 1.5 mL, depending on the specific device. By increasing the fill volume (usually by adding saline) a greater proportion of the medication can be nebulized.[7] For example, with a 1 mL residual volume, a fill of 2 mL would have only 50% of the nebulizer charge available for nebulization, whereas a fill of 4 mL would make 75% of the medication available for nebulization. Many patients use a

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2 mL unit dose of medication in the nebulizer without adding additional saline to optimize fill volume.

Aerosol Size and Airway Deposition

Larger aerosol particles (> 5 μm) tend to impact on the oropharynx, reducing the amount of drug available to the lungs and increasing the potential for adverse effects. This is an important problem in children, who often have high respiratory rates, small airways, and increased air flow turbulence. Efficiency is further reduced if the combination of drug, nebulizer cup, and compressor are not well matched.[6] Droplet size and nebulization times are both inversely proportional to gas flow through the jet. The higher the power-gas flow to the nebulizer the smaller the particle size and the shorter the time required to nebulize the full dose.[3,7] In a lung model simulation of tidal breathing at volumes of 50–400 mL, by increasing the power-gas flow from 4 to 8 L/min the rate of drug output was increased by 264%, but there was only a 32% increase in aerosol concentration.[8] As tidal volume increased from 50 to 400 mL, deposition increased just 2.2–3-fold. The aerosol's mass median aerodynamic diameter (MMAD) was also strongly dependent on air flow. At 4 L/min flow, MMAD was 7.0 μm, with 26.8% of the particles < 5 μm. At 6 L/min the MMAD was 4.9 μm, with 50.1% of the particles < 5 μm. At 8 L/min the MMAD was 3.6 μm, with 70.8% of the particles < 5 μm.[8]

Reisner et al studied air flow from commercially available compressors and from nebulizer-compressor combinations. There were marked differences in flow from the various compressors used for home nebulization.[9] The mean flow from the compressors evaluated without a nebulizer attached ranged from 6.6 L/min to 12.2 L/min. Flow from the nebulizer-compressor combinations ranged from 2.08 L/min to 5.42 L/min. The interaction between flow and device was significant ($p < 0.001$) for the percentage of particles in the respirable range. Thus it is clear that the compressor is as important to aerosol output as is the nebulizer cup. A nebulizer that produces an MMAD of 2.5 μg when driven by a gas source of 50 psi at 8 L/min may produce an MMAD of > 8 μm when operated on a home compressor that produces only 10 psi. This can result in negligible respirable nebulizer output.

Most of the available medication in the nebulizer cup is nebulized in the first few minutes.[2,8] Malone et al found that with 3 different fill volumes, albuterol delivery from the nebulizer declined by half within 20 seconds of the onset of sputtering.[10] The concentration of albuterol in the nebulizer cup increased significantly once the aerosol output declined, and further weight loss in the nebulizer was primarily due to evaporation. Malone et al concluded that aerosolization past the time sputtering began was clinically ineffective.

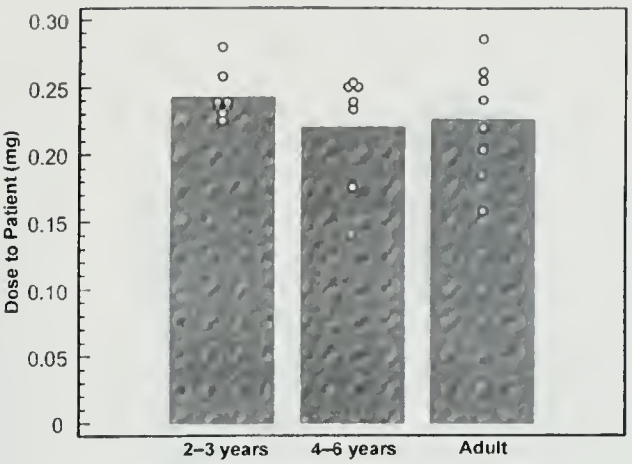

Fig. 1. Dose to patient: mean and individual values in 3 age groups. The 2–3-year-old children used the face mask provided with the Nebuchamber. The older patients inhaled through the mouthpiece, with a nose clip applied. Budesonide was administered as 2 separate doses of 200 μg, with an interval of 45 s. The patients were instructed to inhale each dose from the spacer, using slow tidal breathing for 30 s. The dose to patient was calculated as the delivered dose of the batch measured in vitro from the metered-dose inhaler with adapter, after subtraction of the drug recovered from the equipment, facial tissues, and mouth rinses. (From Reference 12, with permission.)

Special Medication Delivery Issues for Infants and Children

Airway Diameter and Particle Deposition

In infants and small children the airway diameter is small, the breathing rate is fast, nose breathing filters out large particles and thus deposits more medication in the upper airway, and mouthpiece administration often cannot be used effectively.[11] With age, respiratory rate decreases and tidal volume and total lung dose of medication increase. Anhøj et al assessed the systemic exposure to inhaled budesonide from a metered-dose inhaler with Nebuchamber, in patients age 2 years to adulthood.[12] The dose to patient, area-under-the-curve of plasma concentration versus time, and terminal half-life were similar at all ages ($p > 0.35$) (Fig. 1). This suggests that the dose of medication placed in the nebulizer does not need to be adjusted based on the patient's age and that systemic exposure to medication is effectively "regulated" by age-related differences in airway diameter, surface area, and flow.[12]

Patient Cooperation and Aerosol Delivery

Patient cooperation varies with the patient's age and developmental ability.[11,13] The patient-nebulizer interface is critically important for effective medication delivery. For patients who will not hold a mouthpiece but can tol-

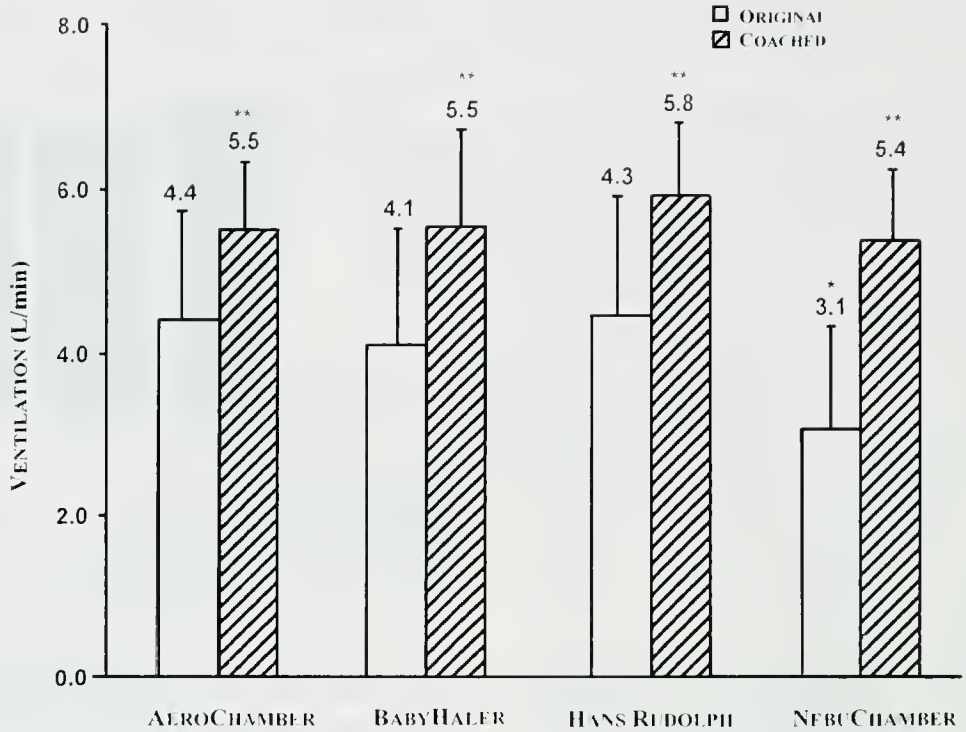

Fig. 2. Face mask leak was studied in vivo with AeroChamber, BabyHaler, Hans Rudolph, and NebuChamber masks by measuring ventilation with an in-line pneumotachograph while the face mask was held in place by experienced parents who were asked to demonstrate how they deliver medication to their children (n = 30; mean ± SD age = 3.2 ± 1.4 y), without any additional instruction. The first 10 patients performed the tests once again within 1 month, while the parents were coached and encouraged to hold the mask tightly against the child's face. The NebuChamber provided the poorest seal, with 45% less ventilation than the AeroChamber mask or Hans Rudolph mask. All ventilatory volumes during the coached session were significantly greater than during the uncoached session. (Redrawn from data in reference 15.)

erate a mask the nebulizer can be fitted to an appropriate aerosol mask. There is no difference in clinical response between mouthpiece and close-fitting mask treatment, so patient preference should guide selection of the device.[14] Mask administration can also be difficult for very young children. Amirav and Newhouse found that of 10 infants who were younger than 2 years, only 3 cooperated fully and consistently with mask aerosol therapy. However, in that study no patient older than 2 years could not consistently perform quiet tidal breathing with a close-fitting mask in place.[15] Amirav and Newhouse also demonstrated that careful training of parents and patients to ensure a good mask seal increases airway deposition from 25–75%, depending on the nebulizer used (Fig. 2) and that increasing the mask leak profoundly decreases aerosol delivery in vitro.[15]

If the patient cannot tolerate a mask treatment (ie, will not wear the mask closely to the face), an alternative commonly employed is the "blow-by" technique, in which the practitioner directs the aerosol from the nebulizer toward the patient's nose and mouth. However, aerosol deposition studies demonstrated that virtually no drug enters the airway with that technique. In a simulation of breathing from a face mask, with a tidal volume of 50 mL and a flow of 8 L/min, Everard et al found that when tubing or face mask was applied to the filter "face," 1.21 mg of a 20 mg sodium cromoglycate fill was deposited. At 1 cm from the filter, 0.49 mg was deposited (a 60% reduction), and at 2 cm distance only 0.18 mg was deposited (an 85% reduction).[8]

Some physicians and therapists counsel parents of infants to "make them cry," based on the mistaken belief that crying will cause the child to inhale the medication more deeply. Crying involves a very rapid inspiration, which causes inertial impaction of the majority of the drug in the oropharynx. The expiratory part of crying is a long exhalation, which loses some of the aerosol that was inhaled. And crying usually prevents a good seal between mask and face, which results in air entrainment, with little or no drug being inhaled. Even if a good seal can be made, the dose inhaled is reduced and the majority of the inhaled dose deposits in the upper airways, to be swallowed. Thus, aerosols should *never* be administered to a crying child.[13,15–17]

Nebulizer therapy works best when a child is quietly breathing. When aerosol is inhaled during tidal breathing

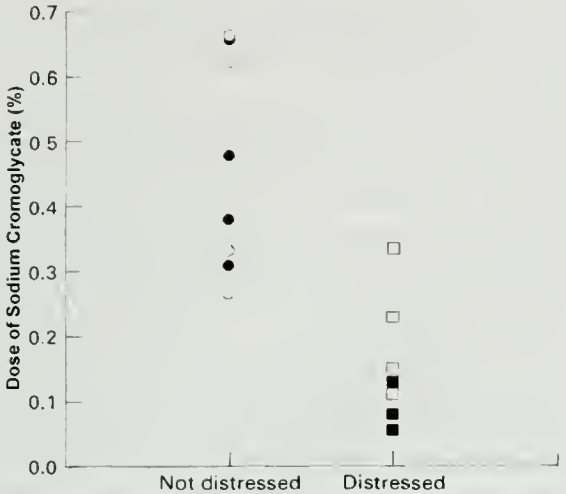

Fig. 3. Estimated absorption of sodium cromoglycate versus degree of infant distress. Fifteen infants were studied; 8 with resolving chronic lung disease of prematurity (mean age 13 mo) (black data points) and 7 with normal birth histories (mean age 11 mo) (open data points). Each was given a dose of 20 mg nebulized sodium cromoglycate, using a Sidestream nebulizer, and distress was graded. Urine was collected for 8 hours and analyzed for excreted drug. Distressed infants absorbed significantly less drug than settled infants ($p < 0.001$). (From Reference 17, with permission).

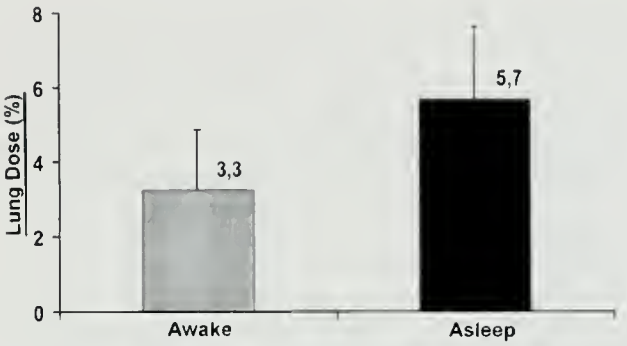

Fig. 4. Lung dose of budesonide delivered via metered-dose inhaler with face mask, while awake and asleep. Data are from 18 infants and young children. Significantly more budesonide was delivered to the lungs during sleep. (Adapted from Reference 18.)

(either awake or asleep), there are good correlations between the dose of aerosol in the lung and both the age and height of the patient ($p < 0.001$). But when aerosol is administered during crying, little is deposited in the lung.[16] With 18 infants, age 9–13 months, Iles et al administered sodium cromoglycate at 6 L/min for 10 min, using a Sidestream nebulizer and a Hudson oxygen face mask held against the face throughout the procedure. Crying decreased lung deposition by 75% (Fig. 3).[17] It is more efficient to deliver aerosol medication via close-fitting mask while the patient is asleep (Fig. 4) than while the patient is awake, even if the patient is cooperative.[18] Janssens attributed this to the more regular respiratory pattern during sleep.

There can also be substantial loss of medication during nebulization while the child is calming down or settling. Because the majority of the medication is nebulized in the first half of nebulization, a parent may incorrectly assume that medication nebulization is constant and therefore that there is plenty of time to get the medication to the child at the end of nebulization, after the child calms.

Care of Nebulizer Equipment

Failure to care for the nebulizer can lead to cracking of the plastic, caking of material within the nebulizer, inefficient operation of valve or baffle systems, and pooling of fluid in the nebulizer cup, with the potential for reduced efficiency and for bacterial colonization and nebulization of the bacteria into the airway.[19–22]

In 1992 Alvine et al found that half of the nebulizer models they tested showed visible signs of malfunction, including spraying of large droplets, leaking of solution, and air leaks that prevented nebulization. Variability of nebulization rate ranged from 57% to 129%. The model with the largest variability was also associated with an unacceptably large variability in particle size. Those results suggest poor quality control by some nebulizer manufacturers.[4] Care must also be taken to maintain nebulizers in good operating condition, which can be difficult with active children in the home.

When nebulizers are properly cleaned between uses, there is no clinically important change in nebulizer performance for up to 100 runs, but unwashed units used to nebulize tobramycin start to fail by 40 runs.[23] Another study demonstrated that inadequate cleaning can decrease nebulizer output by 50%.[24] The Centers for Disease Control and Prevention recommends that nebulizers should be disassembled, cleaned with sterile water, rinsed, and air dried after every use.[19]

Reasons for Nonadherance to Therapy

Nebulizer therapy can be inconvenient for the patient, as it takes more time and requires more complex equipment than a metered-dose inhaler or dry powder inhaler. There are more opportunities for patient error and more excuses for not using a nebulizer, particularly when traveling. Usually nebulizer therapy costs more than metered-dose inhaler or dry powder inhaler therapy, and when cost of medication is a problem, this can lead to nonadherence. Other reasons for nonadherence include the patient not liking the nebulizer, not believing in the use of medications, and nebulization taking too much time.

Patients have reported not using their nebulizers because of concerns about potential adverse effects that they

believe to be associated with medications, such as concern about inhaled corticosteroids and growth, and concerns about "genetic modification of their child" with inhalation of dornase alfa (Pulmozyme). Some parents have also expressed concern that the daily use of aerosol medication can lead the child to become "addicted" to the drug.

In a study designed to evaluate patient characteristics associated with nonadherence to nebulizer therapy, the St George's Respiratory Questionnaire (SGRQ-2) was administered to a cohort of patients with chronic obstructive pulmonary disease and who had been prescribed daily jet nebulizer therapy. The total scores from the SGRQ-2 (higher score meaning greater psychosocial dysfunction) were negatively correlated with adherence, and that association was particularly strong for patients whose scores suggested clinical depression.[25]

An additional problem, more common in the young infant, is the patient being placed on either the wrong medication or on a medication that will have limited or no effect on outcome. For example, many studies have demonstrated that aerosolized β agonists do not improve clinical outcome in patients with bronchiolitis. Paradoxically, changes in the osmolarity of some albuterol nebulizer solutions can actually exacerbate wheezing and lead to reduced pulmonary function in some infants.[26] Furthermore, the use of β agonists in infants with airway malacia (a not-uncommon problem in prematurely born infants who have required intubation for mechanical ventilation) can lead to greater airway collapse and deterioration in pulmonary function. Therefore, failure to respond to medication could be due to inappropriate use of medication, misunderstanding of how to use a nebulizer, failure to use the nebulizer, or the wrong medication.

Patients may also place unexpected things inside the nebulizer. We recently encountered an infant who presented to the emergency department in severe respiratory distress and, upon questioning, the parents revealed that they had rubbed Vicks VapoRub inside the nebulizer before putting albuterol in the nebulizer cup. They had assumed that if the Vicks was helpful when added to a humidifier in the room, that it would provide even greater benefit if added directly to the nebulizer.

Patients will not use a device that they do not like and are not comfortable with, and they may not even use a device that they like. Patient choice is important, but education is critical—not only of the patient but also of the caretakers who train the patients regarding the proper use of nebulizers. In a study comparing the long-term efficacy of personal, video, and group instruction (with a no-instruction control group) for nebulizer use by 152 patients with chronic obstructive pulmonary disease, personal or group instruction produced significantly better nebulizer use and long-term retention of training information. Van der Palen et al concluded that the time spent on patient education was time well spent.[27] In most cases, the best person to do this effectively and accurately is the bedside respiratory therapist.

To improve adherence, aerosol therapy should be administered along with some easily remembered activity of daily living. For twice-daily administration, medications can be kept with the toothbrush and inhaled just before brushing teeth. This will also reduce aerosol deposition in the oropharynx. It is best to avoid the regular use of medication at school, as the inconvenience can significantly reduce adherence and may be an embarrassment to some children. However, the availability of rescue medication at school (or daycare or other caretaker's home) must be assured. It helps to prepare written guidelines for medication use, but the guidelines must be distributed to all places where the child spends time, including home, school, and at the residence of both parents if the parents reside separately.[28]

Summary

Advances in nebulizer design have made them more efficient and "user friendly," but the greatest problem with administering aerosolized medication continues to be educating patients and caregivers to use aerosol devices properly and consistently. Misuse and nonuse are the greatest impediments to effective aerosol delivery. The respiratory pattern and degree of patient cooperation also profoundly affect aerosol deposition, and those effects are greatly magnified in small children. There are many misconceptions about nebulizer use and nebulizer equipment, even in teaching hospitals, and these can have serious consequences when patients do not receive the medication they need. Education is critically important, but unfortunately it is often a misunderstood or neglected part of aerosol administration.

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Discussion

Rau: This issue of "blow-by" just won't seem to go away, and we get questions asking about data on that. Are you aware of any quantification? I have not found any.

Dunne: Mark Everard published extensively on the inefficiency of blow-by, and his 1992 report states that when you remove the nebulizer output 2 cm from the external nose and pharynx, you decrease the efficiency by 85%. So that's taking an already inefficient system and making it more inefficient, and that's why you probably don't see much response with that technique in the pediatric population.

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Barry: About face masks; I think the problem is even more important than you mentioned; not just face mask position. We've got some data currently in press regarding 3 different face masks, and they show that if you choose the wrong one, you can reduce output by 90%. This isn't just a function of the seal or the leak around the face mask; it's due to face mask design. I think this is something that has hardly ever been investigated and needs some more attention.

Rubin: Absolutely. Dead-space volume has been shown to be incredibly important, especially in infants. A child's tidal volume is roughly 7 mL/kg, and if you're dealing with kids under a year old (a 70 mL tidal volume), it takes a few breaths to clear dead space before you even *start* getting drug. And the longer the delay, the more aerosol is going to rain out.

Dunne: Your point about the obstacles to continuous use of aerosol therapy is underscored by White and Sander's survey of parents of asthmatics.[1] Fully two thirds of them indicated that they either "down-dose" or withhold medications, for a variety of reasons; so that's a real important issue, and I agree with the importance you placed on patient and caregiver education. With regard to the fighting and crying toddler, there's a new device, the Westmed Pedi-Neb, that I've seen but haven't had any experience with it. It is a combination of a pacifier and a flange that delivers aerosol to the child's nose while the child is distracted with the pacifier. Do you think there's any lung deposition increase

or any possibility of good deposition with that device?

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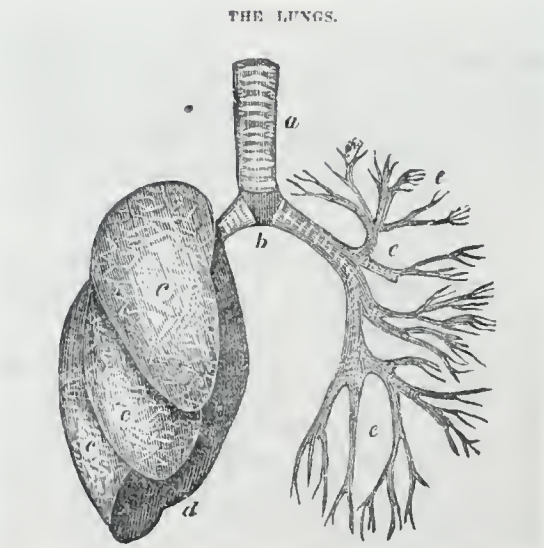
Geller: Betsy McGoogan, a nurse practitioner in West Palm Beach, Florida, saw day in and day out that infants fought with nebulization treatments, so she developed the Pedi-Neb device and found that it was very calming to the babies, and they would take their aerosol. But it directs the aerosol into the nose, not into the mouth, so filtration of drug in the nose may occur. No one knows how much aerosol is filtered out by the nose in infants, though. It's not as good as a tight-fitting mask. We've done some work with it. It's probably intermediate between blow-by and a nice-fitting face mask. What we recommend to parents is that they administer the aerosols while the child is sleeping, and use a mask elbow connector so that it can be directed down while they're supine.



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Economic Aspects of Introducing New Nebulizer Technology

Patrick J Dunne MEd RRT FAARC

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The adoption of new medical technology has been a major factor in the development of today's highly sophisticated health care delivery system. Recently, important breakthroughs in biotechnology have introduced the possibility that certain terminal diseases may soon become a thing of the past. However, these advances have come at a steep price. Total health care spending in the United States is at an all-time high and the rate of increase in annual expenditures is once again in the double-digit neighborhood. It is clear that it will no longer be "business as usual" in health care, especially with regard to the introduction of new technology. New economic realities now require that those advocating the adoption of a new drug, device, or treatment balance their clinical enthusiasm with cost-effectiveness considerations. This is especially important when the cost of a new drug or device is higher than that of existing drugs or devices. Unlike former times, when the decision to adopt new medical technology resided primarily with clinicians, the approval process is now exceedingly more complex and involves many more individuals, some of whom, clinicians and non-clinicians alike, tend to focus more on protecting their budgets than on approving expenditures for new technology. Pharmacoeconomics has emerged to formalize the decision-making process for the adoption of new drugs. Since many of the issues are similar, the basic principles of pharmacoeconomics hold promise for physicians and therapists championing the adoption of new nebulizers. Pharmacoeconomic data, when gathered, reviewed, and presented in a standardized and unbiased manner, can be a valuable tool to help justify the overall cost/benefit advantages of new nebulizer technology. *Key words: nebulization, nebulizer, aerosol, cost-effectiveness, cost/benefit, cost/utility, pharmacoeconomics, economics.* [Respir Care 2002;47(11):1321–1331]

Introduction

The decision to adopt and implement new technology into a health care setting has never been more formidable. In today's environment, health care financial resources are limited, yet demographic, epidemiological, and societal changes are steadily increasing the demand for health care services. The percentage of the total population entering "senior citizen" status is increasing and the elderly are now living longer than ever before (Fig. 1).[2,3] Both of these trends will substantially impact the United States health care delivery system over the next several decades.

Further fueling the increasing demand for health care services is a relatively recent trend to focus on certain chronic medical conditions and the huge financial impact of delivering suboptimal care to that patient population.[4] New care paradigms are emerging that attempt to make individuals afflicted with chronic medical conditions less dependent on acute care, through the active promotion of preventive self care, itself a relatively recent addition to the health care landscape.[5–8]

Accordingly, the demand for health care services nationwide is not expected to abate any time soon. Nor is it likely that a massive infusion of new funding will be forthcoming. Health care providers repeatedly hear that the industry is now expected to "do more with less."

With so many factions competing for limited health care financial resources, clinicians wishing to introduce a new technology or drug face an uphill battle. This is especially true when the technology or drug being targeted for replacement has a long history of perceived successful use and an acquisition cost that, over time, has come to be perceived as relatively inexpensive. When attempting to replace the status quo, proponents will need to overcome initial misgivings by demonstrating superior clinical and financial outcomes with the new drug or device.[9,10]

The new nebulizer technologies discussed during the conference on Liquid Nebulization: Emerging Technologies (proceedings published in this and the following issue of Respiratory Care Journal) are a radical departure from the status quo. They are more efficient, more clinically effective, and will substantially broaden the boundaries of aerosol therapy, to include applications to nonpulmonary systemic conditions (eg, aerosolized insulin for Type 1 insulin-dependent diabetics). This review examines the obstacles and often conflicting issues that must be considered when introducing new, more effective, yet more costly nebulizers. Since there is a lack of relevant data addressing the specific challenge of introducing new nebulizers, I explore the potential advantages of using pharmacoeconomics (long used to justify the adoption of new drugs) to support the introduction of new nebulizers.

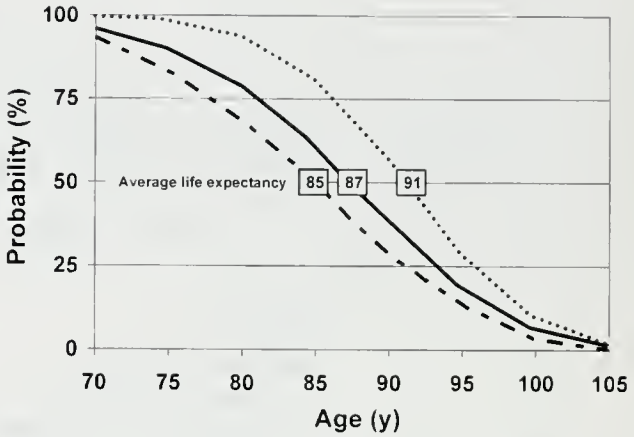

Fig. 1. Probability of a 65-year-old living to various ages. Many people will live 30 years after retiring, and some even longer, as advances in medical technology increase life spans. The percentages are based on the United States Annuity 2000 table. All figures are rounded to the nearest whole number. Man (broken line). Woman (solid line). Couple (dotted line); man and woman; each 65; probability of one surviving. Data from Tillinghast-Towers Perrin consulting firm. (Redrawn using data from Reference 1.)

What Are the Issues?

Though there are numerous issues that must be addressed when introducing new nebulizer technology, the fundamental challenges are quite clear: How to get clinicians to adopt and use a new nebulizer; how to get patients to use the new nebulizer as instructed; how to get institutional gatekeepers to purchase and inventory the new nebulizer; and perhaps most importantly, how to get third-party payors and other reimbursement sources to cover the costs of the new nebulizers. Though the tone of these questions might seem overly commercial to some, the basic message is quite clear: it is one thing to have a new nebulizer that out-performs the current product, but, in today's cost-conscious climate, it is something quite different to convince major stakeholders to accept, adopt, purchase, use, and reimburse for a novel nebulizer, especially when the acquisition cost of the novel product is considerably higher than the device it is in intended to replace.

To provide a framework of strategies and tactics to increase the chances of getting a novel nebulizer adopted,

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Table 1. Five Key Issues in Getting New Nebulizer Technology Introduced

1. Era of limited health care resources
2. Expense of developing new technology
3. Getting new devices approved for use
4. Providing cost/benefit analysis
5. Role of activated consumers

this review identifies 5 key issues that directly impact the adoption process (Table 1). This list of 5 issues is by no means intended to be exhaustive. The complexity of getting definitive decisions made in today's chaotic health care environment requires a focus that allows limited resources to be directed at the most important contingencies. These 5 issues address the overriding concerns that tend to be voiced across several sectors of the health care industry in general and respiratory care in particular. When health care resources are limited, decisions about which care or treatment to fund can be complex, difficult to make, and will, more often than not, involve careful balancing of multiple factors.[11]

Issue 1. Era of Limited Resources

In the United States, as in most other industrialized counties, the size of health care expenditures, as a percentage of the gross domestic product, remains a major concern. Following the 1990s decade of modest, single-digit increases in the rate of health care inflation, the new millennium has witnessed annual increases in the double-digit range—rates of increase last seen during the 1980s.[12] The impact has been felt in corporate boardrooms across the United States and in the halls of both federal and state government buildings. Consumers of health care services are likewise feeling the impact, as traditional coverage and eligibility options shrink while annual premiums, deductibles, and copayments escalate.[13] Health care strategists and policy makers are faced with the reality that substantial additional funding increases are unlikely.

Yet, for a variety of reasons, the overall demand for health care services steadily increases, adding further strain to an already stressed industry. Improved longevity, an aging population, and improved mortality across all age groups have each exerted an influence. Not surprisingly, politicians are once again talking about the need to fix the still-ailing health care system. However, history demonstrates that bipartisan political rhetoric seldom (if ever) translates to meaningful improvement, especially in the complex, heavily tradition-bound, and often anachronistic United States health care industry. Health care providers have learned all too well that it is better to rely on their own initiatives rather than to wait for political solutions. One step in this direction is a renewed interest in revisiting how certain medical conditions are handled.

Under the traditional approach to providing health care in the United States, individuals with chronic medical conditions are more likely to seek and receive treatment only at times of acute exacerbation.[4–5] This "episodic approach" to treating chronic medical conditions is now perceived as wasteful, especially in light of the frequency of repeat visits to acute care settings so common in that patient population. Many now believe that a more proactive, consumer-based, preventive approach would alter this "revolving door" syndrome.[4] With chronic medical conditions so pervasive in the United States, greater attention is being directed toward disease state management programs, further fueling the increased demand.

As a result of these and other economic pressures, a "cost-reduction" mindset is now pervasive throughout the United States health care system. It is an instinctive reaction to loudly voiced concerns of the need to curtail double-digit increases in the annual growth rate of health care expenditures. Such a mindset tends to promote the notion that the least costly care is the ideal. Unfortunately, experience has shown that seeking the least costly care is, in reality, often more of a short-term solution. Short-term fixes do indeed provide the opportunity to quickly demonstrate immediate cost-savings, but such a mentality often obscures the vision of a much larger and longer-lasting positive impact that can accompany the introduction of newer care and treatment modalities.

The added expense of new care and treatment modalities is viewed in the present context as "nice but too costly." Those attempting to champion the introduction of new nebulizers must be prepared to address the pervasive mindset that new modalities might not be justifiable in the present era of cost containment. In these and other similar circumstances, the challenge is to effectively convey the notion that increased costs today easily translate to considerable savings tomorrow. Given the widespread economic pressures to contain spending, this will be no easy task. Nonetheless, the overall improvements to the health care delivery system that might be seen with such a broad perspective and vision are intriguing indeed.

Issue 2. Expense of New Technology

The development of new medical technology represents a major investment for pharmaceutical and device manufacturers. To begin, considerable expense is required to secure and protect the intellectual property that underlies a proposed new drug or device. Additional expenses are then required for research and development to determine the feasibility and potential application of the new drug or device. Assuming initial research and development results are favorable, efforts are eventually directed at creating

working formulations or prototypes to determine if the intended product can realistically be manufactured in a reliable and cost-effective manner. Clinical trials are undertaken to determine the clinical efficacy and safety of the proposed new device or drug over the range of intended applications.

Data collected from the initial clinical studies are often submitted as part of the process of obtaining regulatory approval to manufacture and distribute the new drug or device to the medical community. The United States Food and Drug Administration (FDA) scrutinizes submitted data from one or more controlled clinical trials to determine if evidence is sufficient to establish safety and efficacy. It is not uncommon for the FDA to request supplemental data, possibly even data from additional clinical trials, before a favorable determination is made. Obtaining FDA approval is a considerable expense, often rivaling or even exceeding the combined costs of protecting intellectual property and research and development. Moreover, it may take months, possibly even years, to obtain FDA approval.

During this entire process the manufacturer receives no income from the product under development. Instead, development costs are often funded by revenue from the sale of existing products. In some cases the developing company must fund some or all of the new product development with investment capital, and the addition of outside investors comes at a steep price, especially for smaller companies. This approach usually involves the dilution of equity held by people who made a considerable investment of capital or "sweat equity" at the start of the process. One way or another, the developing company has made a formidable investment and has heavily mortgaged the future on an idea that has yet to generate any income. It is not uncommon for a pharmaceutical manufacturer to spend upwards of $800 million to successfully bring one new drug to market.[14]

It is therefore not surprising that manufacturers of new medical technology are eager to bring a novel drug or device to market as quickly as possible following regulatory approval, and rightly so. There is a legitimate sense of urgency to show a positive return on a large investment. As such, the manufacturer will expend considerable resources to market the new drug or device, to get the medical community to take notice. Clinicians practicing in a sector where the new device or drug has immediate relevance are contacted and informed about the advantages of the new drug or device. However, in today's cost-conscious environment, clinicians alone may no longer be in a position to effectively get a new drug or device adopted, so manufacturers are compelled to develop additional strategies.

One such alternative route toward getting institutional approval of a new drug or device is to undertake collaborations with interested clinicians within an institution, to generate accurate and reliable data that can be used to justify the additional expense to one or more skeptical institutional budget watchers. Such collaborative trials and studies are becoming increasingly popular. Admittedly, even with the best intentions this manufacturer support does introduce the potential for bias, but this limitation can be successfully addressed from the outset. Industry-sponsored trials and studies will continue to be quite prevalent throughout health care. Instead of summarily dismissing the utility of industry-sponsored studies, skeptics would be better served to work more closely with industry to help address perceived weaknesses or limitations. The better the data, the better the quality of care and treatment decisions.

Issue 3. Getting New Technology Accepted

Attempting to introduce new technology in today's somewhat chaotic health care delivery climate is a highly complex process with numerous contingencies. Unlike the heyday of the 1980s, clinicians alone are no longer the sole decision-makers. The rise of prospective payment and the widespread proliferation during the 1990s of risk-sharing managed-care programs created many additional affected stakeholders and decision-makers, many of whom are nonclinicians. Health care executives, administrators, directors, and other nonclinicians, including clinicians who have assumed nonclinical roles and responsibilities, are now conditioned to instinctively focus on the financial impact of most proposed new technology. Initial reflexive skepticism must be anticipated and proactively addressed.

Though it might be obvious to clinicians that a certain new drug or device does indeed represent a definable clinical improvement over existing practices, that will not, in and of itself, guarantee adoption. The new focus on the economic impact over the clinical impact has given rise to an attitude that is best described as "provincial budget protectionism." Continual reminders and pressures to control costs only tend to reinforce this attitude. Provincial budget protectionism gives rise to boilerplate responses to proposed new technology, such as: "I'm not convinced it's any better," or "We can't afford it," or "The added costs are not justified." Sometimes the pat responses are a little more palatable, but dismissive nonetheless: "It looks pretty good, but we'll need more evidence," or "We need to wait and see if it really works," or "It is something we should look at but we have other priorities right now." Admittedly there is often a measure of truth to all of those statements, but there is also the risk that such reticence will deter otherwise enthusiastic clinicians from advancing innovative treatment and care strategies.

Depending on the new product being proposed, such statements are now routinely voiced by one or more of the following decision-makers: purchasing agents, medical di-

rectors, administrators, department directors, benefits managers, case managers, and often members of hospital or health plan pharmaceutical and therapeutic committees. In essence, there is an initial visceral response to focus on the short-term financial impact of new technology, at the expense of longer-term outcomes. In the interest of fairness, this inherent reticence may even be based on what is perceived as a reasonable appreciation of the realities of today's limitations. Good intentions notwithstanding, certain decision-makers have erected formidable barriers to the adoption of new technology. Proponents of new technology will need to be, above all else, persistent and armed with relevant, evidence-based data.

Issue 4. Providing Cost/Benefit Analysis

If budget gatekeepers and other key decision-makers are to be won over, the proponents of the new product need a strategic plan to gather and present empirical evidence that demonstrates better outcomes. Valid and reliable data that demonstrate both clinical improvement and overall cost-effectiveness will greatly enhance the likelihood that the new technology will be seriously considered. Moreover, the data used to support the adoption of the new technology must be easily understood by all, especially nonclinicians. If financial modeling is used, the assumptions must be representative of the "real world" and not hypothetical situations based on supposition and wishful thinking. The stakes are simply too great to expect anything less.

A major challenge facing clinicians in this era of cost-containment is a lack of resources to conduct serious investigations to evaluate the impact of new technology. As a result, it is often left to the manufacturer to fund or otherwise support (eg, by providing free goods) the data collection efforts. This of course introduces a potential for bias, intentional or otherwise, that can skew the design and results. The best possible scenario, but least practical in an era of limited resources, would be for interested clinicians and institutions to independently conduct parallel trials to see if their outcomes are similar, but logistics alone precludes such an approach. Nonetheless, manufacturers have a vested interest in moving the validation process along quickly. The challenge is to work with interested and motivated manufacturers while ensuring that clinical credibility is maintained.

When the results of investigations or trials are considered specious or otherwise self-serving, a credibility issue is introduced that may have serious long-term adverse consequences. It is therefore imperative that it be done right the first time. Those coordinating and participating in such trials will be expected to maintain an objective focus in terms of what will be evaluated and by whom. Of equal importance will be the need for a clear understanding and agreement as to how, when, and under what conditions the investigation will be conducted. The collection and reporting of outcome data must follow a predetermined scheme to ensure not only credibility but confidence.

Issue 5. Impact of Activated Consumers

One of the key changes being promoted for an improved, less wasteful future health care delivery system is the active involvement of patient-consumers in the decision-making process. As it is, patient-consumers are already being forced to become more active participants in their health care decisions.[7,15,16] Out-of-pocket expenses are steadily increasing as annual deductibles and copayments escalate. Patient-customers also face increased out-of-pocket expenses when they decide to seek health care from nonparticipating providers, as is often the case when the health care benefit package offered by an employer is a generic, no-frills, managed-care product. In that situation the patient-consumers may find their health care needs not effectively met within the approved panel of providers, forcing them to seek care from nonparticipating providers.

There are several other forces at work that will result in patient-consumers becoming more directly involved in their health care choices. A major change is already underway in the administration of health insurance benefits, as employers reevaluate the traditional model for providing health care benefits. Historically, health care benefits have been provided to an employee as a "defined benefit."[16] Under that concept, employers negotiate the most affordable health care benefits package for their employees and then pay the selected health plan the agreed rate. Employees have little say over the selection of the health plan. If and when employees or their covered dependents encounter difficulties in obtaining the level of health care they have come to expect, complaints are soon directed at the employer's benefits manager for contracting with a health plan that is now perceived as unacceptable. The relationship between the employer and employee becomes tense and is especially troublesome when collective bargaining is also added to the mix.

To remove themselves from the ire of employees disgruntled with the selected health plan, employers have begun adopting a new concept for providing health care benefits, known as "defined contribution."[16–18] Under this model, employers contribute a defined amount of money per employee to allow each employee to purchase his or her own health care benefits. The defined contribution approach compels employees to evaluate competing health plans to see which one will best meet their needs. Once selected, the employer pays the premium to the health plan on behalf of the employee. If the employee encounters obstacles to access or coverage, the employer is off the hook. Under a defined contribution model, consumers soon

realize the importance of the age-old axiom, "Let the buyer beware."

One of the big unknowns in having consumers assume a greater role in health care decisions is the potential for increased tensions between patients, providers, and health plan representatives.[7] Generally, patient-consumers initially lack the insight and background about the consequences of a particular disease or condition and often have unrealistic expectations about what interventions will work and the time frame for clinical and functional improvement. Perceptions tend to be formed from a combination of limited knowledge, wishful thinking, and misinformation gleaned from one or more sources: print media, the Internet, or fictional depictions seen in film or video.

Another factor driving consumer activation is direct-to-consumer advertising for prescription drugs. Hundreds of millions of advertising dollars are spent each year encouraging consumers to actively approach their physicians to determine if the drug or product being promoted is "right for you." Physicians, already under tremendous pressures to tend to a burgeoning schedule of office visits, are not inclined to spend valuable time discussing the indications, effects, and clinical uses of heavily promoted prescription drugs.[19]

Such efforts to activate consumers create the risk that a patient-consumer might not accept a legitimate medical explanation that contradicts what he or she believes. For example, a physician specialist may be correctly managing a chronic pulmonary condition, including prescribing a standard compressor-nebulizer for self-administration of aerosolized medications, but the patient-consumer may want one of the new, portable, battery-powered nebulizers, the one they saw a friend using or saw in a magazine or read about on the Internet. The patient-customer is swayed by the enhanced portability, whereas the prescribing physician knows that only the standard electrical compressor will be covered under the health plan, which would certainly favor the less expensive electrical compressor as the most cost-effective option and consider the new, battery-operated nebulizer more of a convenience item. At the same time, the patient-consumer (or possibly even the prescribing physician) is convinced the battery-operated feature is indeed medically necessary. Such disagreements about what is medically necessary (covered) and what is a convenience item (noncovered) will only intensify as patient-consumers become more involved in their health care decision-making. Extending patient-customers the option of paying privately for items they perceive as medically necessary but that the health plan refuses to cover adds fuel to the fire.

In summary then, the above listed 5 issues are the key obstacles that are sure to emerge as new nebulizer designs are introduced to the marketplace. Those interested in championing the adoption of new nebulizers will be well advised to address each of these issues beforehand, in a thoughtful, deliberative manner. Relying solely on the features and benefits of a novel nebulizer design to justify its adoption will not work in today's environment. Since there is little written about the specific challenge of introducing a new nebulizer into a marketplace consumed with a cost-containment fervor, it may be helpful to look at what has been written about getting a new drug adopted in that environment.

Table 2. Types of Economic Analysis

Type	Outcome
Cost minimization	Select product with lowest cost
Cost-effectiveness	Cost per number of cures or lives saved
Cost/benefit	Costs versus overall savings
Cost/utility	Cost per quality-adjusted life year

(Adapted from Reference 16.)

Pharmacoeconomics: Just for New Drugs?

Pharmacoeconomics is a relatively new but rapidly growing field. Long the purview of the pharmacy profession, pharmacoeconomics represents a formalized, disciplined process to evaluate the cost-effectiveness of new medications. The purpose is to provide an objective framework for making clinical, therapeutic, and care decisions.[20] No doubt, the growing popularity of using pharmacoeconomic data and related outcomes to justify the replacement of an existing formulary medication with a new agent is being driven by the economic realities associated with an era of finite health care dollars.[21]

A major challenge facing individuals collecting and presenting pharmacoeconomic and outcome data is to ensure that the evaluation process focuses on the *net outcomes*, over time, instead of just looking at the immediate incremental increases in unit cost.[22] Provincial budget protectionism tends to elevate the issue of incremental cost increases to the primary point of contention. In that context, efforts to justify adoption of a new technology are extremely difficult if not futile. Those championing new technology must understand the ways economic data are collected, presented, and perceived by key decision-makers.[23]

Types of Economic Analysis

There is a hierarchy of 4 types of economic analysis that can be used to conduct pharmacoeconomic studies (Table 2).[16,20] Each type has its own limitations, usefulness, and relevance. A brief description of each follows.

Cost Minimization Analysis

Cost minimization analysis occurs when there is a direct comparison of 2 drugs (or devices) assumed to have identical outcomes, tolerability, and adverse effect profiles.[21] In this situation the decision is rather straightforward: the drug or device having the lowest acquisition cost is preferred. This should be the only situation in which a decision to adopt a new drug (or device) can be predicated on cost alone. In reality there are relatively few situations in today's health care system in which the basic assumptions underlying cost minimization studies would be applicable. The more common situation is for differences to exist between the drugs being compared, including acquisition costs. For this and other reasons, cost minimization analysis is not widely used.[21–25]

Cost-Effectiveness Analysis

Cost-effectiveness analysis assesses the health care benefit(s) of an intervention by considering one or more outcomes and comparing the observed outcomes with the costs of the new drug. Outcomes are typically expressed as some tangible benefit directly attributable to the intervention, such as a reduction in the overall number of treatments, the number of hospital admissions avoided, or decreases in length of stay. Because of their immediate obviousness and relevance, outcomes associated with cost-effectiveness analysis tend to be readily understood by clinicians. However, cost-effectiveness outcomes might not always be translated to a dollar value, and in the present climate that omission greatly reduces the utility of such data. This limitation is more adequately addressed in the next type of analysis, the cost/benefit approach, in which cost-effectiveness data are viewed in the context of economic benefits.

Cost/Benefit Analysis

Cost/benefit analysis attempts to translate into dollar terms the improved clinical outcomes from a new care or treatment intervention. One substantial challenge in cost/benefit analysis is that certain cost estimates, especially indirect costs are, by nature, arbitrary. Though charges for costs of goods and some services are relatively easy to identify, it is more difficult to quantify certain costs, such as labor, benefits, administrative overhead, and regulatory compliance. Nonetheless, attempts to evaluate costs will be expected to address both direct and indirect costs. For example, if a novel nebulizer is shown to result in 35% fewer treatments during a hospitalization, the incremental increase in the cost of the device should be evaluated in the context of the overall savings realized. In that context fewer nebulizer treatments during a hospital stay might ostensibly result in more satisfactory patient care, fewer missed treatments, labor savings, and possibly a decrease in the length of stay. Taken together, the overall savings might more than offset the higher acquisition cost of the new nebulizer.

Cost/benefit analysis, by design, requires that clinicians approach this type of study or trial with an understanding that economic end points are included in the study design. Capturing and blending cost-effectiveness data with valid cost/benefit outcomes data helps decision-makers see the larger picture.

Cost/Utility Analysis

Cost/utility analysis attempts to combine outcomes from clinical studies into a discreet measurable ratio.[20,21] Designing and conducting pharmacoeconomic studies using cost/utility analysis is the most complex of the 4 approaches, and an in-depth discussion is beyond the scope here.[25–27]

The common measure used in cost/utility analysis is called "quality-adjusted life years" (QALYs), a term which combines several elements, including length of survival, morbidity and mortality, and perceptions of well-being into a single common unit. The basis of cost/utility analysis is to have the patient (or caregiver) assign a utility value to a health state, on a scale of 0–1, in which 0 utility represents being near death and 1 represents perfect health. For example, if a given health state has a utility of 0.5, a year spent in that health state would be worth 0.5 QALY. By comparing the cost of treatment to the number of QALYs saved, a cost/utility ratio can be calculated.

Cost/utility ratios are theoretically the most standard of all ratios used in pharmacoeconomic studies. Cost/utility study methodology allows several care and treatment interventions to be evaluated concurrently. Hence, their greatest appeal is for difficult broad policy and resource allocations decisions.[20]

Types of Pharmacoeconomic Studies

When a decision is made to formally evaluate a new drug, 4 methodologies can be considered,[20] each of which have certain strengths and limitations. To ensure the outcomes will be useful and acceptable, those involved in preparing and conducting such studies will be expected to clearly appreciate the differences between the competing strategies.

Prospective Economic Trial

A prospective economic trial focuses almost exclusively on economic variables and typically consists of relatively routine, straightforward interventions[20,21] such as comparing one drug or device with another in a comparable set-

ting and measuring economic outcomes. The difficulty with this approach is that there are wide differences, even within the same institution, in how cost variables are reported. Accordingly, the trial must enroll a very large sample size if significant differences are to be detected, making this an expensive and time-consuming approach. For these and other reasons, prospective economic trials alone are not widely used in pharmacoeconomic studies.

Piggyback Trial

The "piggyback" trial, which is gaining in popularity, uses a clinical study as the basis for measuring additional economic variables. For example, a clinical study may reveal that a new drug has superior efficacy and an acceptable safety profile. The clinical markers would include one or more specific improvements observed following administration of the new drug (eg, a 30% increase in forced expiratory volume in the first second). In this case, secondary economic markers could also be identified and appropriate data collected and reviewed. The improved clinical efficacy might reduce the number of asthma patients admitted to the hospital from the emergency room. Another economic marker might be fewer physician visits during the asthma season.

At the conclusion of a piggyback study, a better clinical efficacy and safety profile could be established. At the same time, both direct and indirect economic data can be collected and compared. If the clinical trial is properly powered, the results could be used to guide decisions about adopting the new drug, justifying the higher acquisition cost.

There is an important point that must be considered whenever data from clinical studies are later used to justify adoption of a new drug. The natural inclination is to use existing clinical data that were originally generated to satisfy regulatory requirements such as obtaining FDA approval. However, clinical studies undertaken to support an application for formal approval are limited in focus.[28,29] The primary emphasis during FDA trials is to establish the efficacy and safety of new drugs or devices. Rarely will that sort of data address economic issues regarding widespread use once approval is obtained. Thus, subsequent clinical studies must address economic issues once the new drug or device is approved. Manufacturers are under tremendous pressure to realize revenue from the sale of newly approved drugs and devices, but additional studies addressing the economic impact of adopting the new drug and device will be needed and expected.

Review of an Existing Database

Though it is intriguing to search the extensive databases that exist in health plans, managed-care programs, and elsewhere, this approach does present a serious obstacle. Retrospective studies present the inherent weakness of not being able to randomize patients or establish a definite causal relationship between different interventions. However, this approach might prove useful in establishing a baseline against which to compare subsequent outcome studies. As an example, one could review a database and determine the incidence of chronic obstructive pulmonary disease patients who require hospitalization for respiratory-related problems during the flu season. Those data could then serve as the historical standard to compare with admission data from a piggyback study primarily designed to look at 2 different drugs.

Database reviews cannot be used as the sole method of gathering valid and reliable pharmacoeconomic data. Data reliability from large health care databases is somewhat suspect because of the numerous individuals and sources inputing data into the system and the fact that an unknown number have direct access following the initial data input. However, large health care databases will probably become more reliable with advances in information technology and as access, confidentiality, and privacy guidelines mandated by the Health Insurance Portability and Accountability Act are implemented throughout health care.

Modeling

The creation and use of models and simulations to demonstrate cost-effectiveness is quite popular in health care, especially with manufacturers. Basic assumptions are used to develop a simulation in which potential customers see a visual representation of how a new drug or device will compare to the existing drug or device. Economic and utilization assumptions are used as the basis for capturing existing costs (direct and indirect) and the allocation of resources for a given clinical situation. Data are furnished by the potential customer and inserted into the model. Once the program is completed, the manufacturer hopes that the results will prove that the new drug or device is a better deal than what is currently in use.

The main difficulty with modeling, especially when designed and developed by industry, is that the assumptions may be more idealistic than realistic. The challenge is made all the more difficult because there is so much variation throughout health care, and the variability is not just due to geographic differences. It is not uncommon for 2 facilities in the same city, separated by only a few miles, to have different approaches to providing care and treatment. Economic and utilization assumptions that may be accurate for one or several institutions may be completely irrelevant in other institutions. Accordingly, at the outset, those involved in the process must recognize the limitations of modeling, especially with respect to the validity of

the underlying assumptions and their relevance to various settings.

To summarize, several types of pharmacoeconomic analysis and evaluative study are useful in the arduous process of justifying the adoption of a new and possibly more expensive drug. Upon review of the basic underlying principles of pharmacoeconomics, it appears that pharmacoeconomics could easily work with a new nebulizer as well. Clinicians should consider this option when enthusiasm for the positive clinical impact of adopting a new nebulizer begins to emerge.

It is important that those involved with designing and conducting such analysis remain sensitive to the various limitations associated with each strategy. It has been suggested that a valid and reliable economic evaluation has several essential components:

1. Relevant, good quality clinical data from a robust study design
2. Relevant outcomes and costs that are measured, valued, and, if appropriate, also discounted credibly and accurately
3. Appropriate data analysis methods
4. Upon completion of the study, presentation of the results in a manner that maximizes their usefulness[23]

Obstacles to New Nebulizer Technology

One of the major challenges to introducing a new nebulizer is the long legacy of existing devices. Standard jet nebulizers in use today are relatively inexpensive and, in spite of recognized limitations, have for decades been used successfully in most clinical settings. One troubling limitation is the erosion of performance in a single-patient-use nebulizer when used for extended periods, such as occurs with home use. In the hospital this weakness is addressed by replacing the nebulizer every few days. Another weakness of conventional jet nebulizers is the inefficiency of medication deposition in the lungs, which is usually $< 20\%$ of the nebulized dose. However, this limitation has been addressed by having a higher dose of the medication in the nebulizer formulation than in other formulations, such as that in a metered-dose inhaler. Obviously, improved performance and drug delivery should translate to better clinical outcomes, and one would hope that improved performance and drug delivery would be welcomed, but cost will remain a lingering concern until empirical evidence shows long-term financial benefits.[30]

Provider acquisition costs are nominal for standard, single-patient-use jet nebulizers. With the proliferation of group purchasing agreements and other bundling incentives the unit cost has steadily fallen, to the point where it now is less than a dollar. Newer, more efficient devices such as breath-enhanced and breath-actuated nebulizers cost substantially more, and the new portable electronic nebulizers can cost several hundred dollars. A standard compressor-nebulizer costs about $50, so that cost difference is certain to raise concern.

Thus, the low acquisition cost and widespread acceptance of the performance limitations of conventional jet nebulizers are potential obstacles to the adoption of a novel nebulizer. Clinicians with recognized expertise in therapeutic aerosols, primarily respiratory therapists (RTs), must assume a leadership role in evaluating whether the higher acquisition cost of a novel nebulizer (or drug) is justified in the long term by improved clinical, functional, and fiscal outcomes. But that may be easier said than done.

Another challenge faced by those eager to introduce novel nebulizers into the clinical setting seems to be provider indifference. Increasingly, providers (RTs among many others) are faced with burgeoning workloads caused by personnel shortages. It is not surprising then that RTs are not initially as enthusiastic as manufacturers would like about championing new nebulizer technology. There are simply too many other demands on an already full schedule. The challenge is to elevate awareness of the potential impact of new nebulizer technology and how its adoption might enhance clinical efficiency. When the data are compelling, RTs have a rich legacy of advocating the adoption of new technology. The profession has repeatedly learned that, in the long term, the results of innovation were well worth the effort.

In the 1980s many RTs became very interested in nebulizer design and performance because of concern about clinician exposure to potentially harmful aerosol exhausts from nebulization of pentamidine and ribavirin.[31] As a result, nebulizers with integral scavenging filters soon became the norm when either of those agents were administered. Today the clinician exposure issue has returned, as aerosol therapy is being expanded to include the delivery of potent systemic agents (eg, aerosolized chemotherapy). It was recently reported that passive exposure of RTs to the exhaust of nebulized racemic albuterol resulted in detectible elevation in the plasma level of the nontherapeutic (S) isomer.[32] Previously, several investigators studied the purported higher incidence of occupational asthma in RTs.[33,34] Clearly, the entire issue of provider protection during aerosol therapy warrants further attention. The use of more efficient nebulizers to improve drug delivery and minimize caregiver exposure to aerosol exhaust is an important issue that remains to be explored.

Whether motivated by the prospect of more effective treatments and better patient outcomes or concern for their personal safety, or both, RTs are the best suited providers to study and evaluate if adoption of newer, more costly nebulizers and medications can be justified. Given today's unsettling health care delivery environment, that will be no easy task. Nonetheless, the preliminary evidence does suggest that new nebulizers can improve efficiency, effective-

ness, and safety, so RTs should pay serious attention to the potential benefits to patients and not be deterred by the initial misgivings of those whose decision-making is guided by provincial budget protectionism.

Justifying Value: Some Caveats

Manufacturers preparing to introduce a new nebulizer or drug into the clinical setting face formidable challenges. The present health care environment is permeated with a cost-consciousness mindset that often becomes the dominant force behind most care and treatment decisions. This is especially unsettling when such decisions are based on the perceived negative consequences of the "here and now" (ie, it costs more) instead of the positive effects that might accrue as a result of adopting new technology (ie, better overall cost-effectiveness).

Clinicians eager to champion the adoption of new nebulizers have much to benefit from the field of pharmacoeconomics. The formalized methodology provides a framework in which cost and benefit data can be accumulated and used to support the most appropriate clinical decisions. The more robust the study design, the more credible the outcomes, and (assuming the data support the new intervention) the greater the probability that the right decision will be made for the right reasons. Often it is necessary to balance the desires of one constituency with those of another, but potential or actual bias must be avoided to ensure objectivity. Industry-sponsored studies are especially prone to being dismissed as too self-serving, especially when the provincial budget is to be protected at all costs.

Mindful of the importance of data that pharmacoeconomic studies can generate, a formal movement is underway to disseminate "generally accepted pharmacoeconomic principles,"[35] and a code of ethics has been developed. These efforts are intended to minimize the occurrence of biased and self-serving pharmacoeconomic studies, thereby enhancing the utility of data from quality studies. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR), a relatively new professional organization, has taken the lead in this endeavor.[36] The ISPOR has quickly become a driving force in the pursuit of valid and reliable research data that can be used to make more informed and hopefully more equitable care and treatment decisions.

The ISPOR's stated purpose is "to translate pharmacoeconomics and outcomes research into practice to ensure that society allocates scarce health care resources wisely, fairly, and efficiently."[36] In a word, the ISPOR strategy is to advance the "science" of pharmacoeconomics and health outcomes research. The mere existence of the ISPOR underscores the fact that the growing need for quality data upon which future care and treatment decisions can be made is not just limited to the United States. The reality of finite health care resources necessitating hard decisions faces countries worldwide.[37,38]

Summary

The development and availability of new nebulizers has the potential to greatly improve the administration of therapeutic aerosols. These new devices will also bring closer the possibility of aerosol therapy for nonpulmonary conditions in a more comfortable, convenient, and one would hope more efficacious manner. As with any new technology there will be those who immediately see the short and long term advantages of a new nebulizer and will be motivated to champion its adoption. At the same time there will be others who view a more expensive nebulizer with skepticism. In the present environment that lack of instant acceptance is to be expected. When the skeptics outnumber the champions, the chances for adoption diminish. It will be up to the champions to gather and present data that are credible, compelling, and easily understood. To that end, industry can play an important supportive role. There is the potential for bias and distortion of methodology and results, but if all parties abide by the generally accepted pharmacoeconomic principles and the ISPOR code of conduct, clinical studies and trials will have a much better chance of being accepted by skeptical decision-makers. Care and treatment decisions will then be made on the basis of good data, even if adoption of a new drug or device drives up the immediate acquisition costs over historical levels. If adoption of a new nebulizer results in more cost-effective outcomes through reduced complications, improved efficiency, or more appropriate utilization, then it will be well worth the higher unit cost. At the same time, expending additional energy and effort to properly gather data supporting the adoption of a new nebulizer will be well worth the investment. Ideally, better respiratory care will result. Hopefully, in the long run, it will be proven that better health care, not necessarily cheaper health care, will save both lives and money.

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Discussion

MacIntyre: Thank you, Patrick. That was a different look at things for a conference such as this one. One of the things that has always bothered me about cost/benefit analysis in health care is that I've never figured out how you can assess cost/benefit for an expensive new drug that saves lives but also drives up the cost of health care. An extreme example of this problem is that the cheapest way to take care of an intensive care unit patient is to kill him on the first day. And so anything you spend to avoid a first-day death will certainly drive up the cost of that person's care. Taking it a step further, somebody once told me that every hospital discharge is a guaranteed hospital readmission at some point down the road. So if you got rid of them on that first hospital admission, you'd take care of a future one later on. I'm being a little bit cynical here, but I've often had a great deal of difficulty trying to translate a beneficial health care outcome—survival, a return to see the grandkids, and things like that—in some kind of economic terms, because it *always* costs money.

Dunne: I'm not a total expert in pharmacoeconomics, but I think quality-adjusted life years is an element we need to look at. It is very difficult to get people to agree on what the variables and the fixed elements should be in the formula for quality-adjusted life years. I'm also concerned that there are a lot of people, even within our own ranks, who sometimes miss the bigger picture. I've heard respiratory therapists say, "Well, if I use that new nebulizer it'll cut down the treatment time, and that means I'll lose my job!" To which I say, "There are going to be plenty of respiratory patients, you're going to be expected to do more as the number of patients increases, and do you know that there's a shortage of qualified people entering the field?"

O'Riordan: There is a lot of literature on cost-effectiveness in asthma. For example, the pharmaceutical industry has worked for HMOs [health-maintenance organizations] in studying inhaled steroids for asthma management, and have demonstrated that the HMOs spent less money per patient when the patients were treated properly.

Dunne: Yes. There's no question, especially in the pediatric population,

that inhaled steroids are very, very effective. They have been successful, but those are well designed studies, and they certainly are on the cutting edge of pharmacoeconomies.

MacIntyre: I agree with you that it works in a disease like asthma, where if you treat them better you keep them out of the hospital and they live productive lives. But it's hard to say that that works every time. The new sepsis drug is a great example: it's 6 or 7 thousand dollars a pop and it'll save 1 out of 16 that you treat, which means that you treat 16 to save 1, and that person you save is probably an elderly patient who has chronic diseases and is going to consume a lot of health care resources as a consequence of being saved. I still would argue that we *should* be saving them, because they're human beings and we value human life. The problem is that that value on human life certainly does not translate well into dollars.

Rubin: Patrick, I want to add something to what you said about respiratory therapists' job security. Job security isn't in the number of patients or the number of treatments, but in respiratory therapists acting as professionals and doing patient education. The respiratory therapist's role today is to educate patients. That's why they need to be knowledgeable about devices, medications, and techniques of medication administration and therapy. Education is what they should be doing at the bedside while they're delivering therapy. That's something they should assume as professionals. The more they know, the more they learn, the more they teach, the better off they will be. That's their true job security.

Dunne: I totally agree. Patient education is so important, but it often seems to take a back seat to other activities. My own observation is that hospitals that have gone to 12-hour shifts tend to have staff morale problems. I know that decision is made for the right reasons, but I'm not so sure it's the best thing that's ever happened to the health care work force.

Dolovich: Over the last 15 years or so a number of analyses have been done of the cost of the metered-dose inhaler [MDI] with spacer versus nebulizer, particularly for in-hospital use. The balance sheet comes out in favor of the MDI. I wonder how that fits in with your attempts to indicate to these various organizations that fund these different devices that the new nebulizers should be viewed as replacements for the MDI, because they are metered-dose *liquid* inhalers. The equivalent treatment for bronchodilators and corticosteroids can be given in a similar way to the MDI.

Dunne: I think that if the decision-makers had their choice, MDIs would rule the world. Medicare decided in the 1990s that they did not want to pay for all the solutions that were being put into those Medicare nebulizers. Interestingly enough, those same solutions, when put into an MDI, were considered *drugs*, and Medicare didn't pay for them. So Medicare had a vested interest in promoting MDIs. What they basically did was to put the burden back on the physician, and said, "For Medicare to cover this compressor/nebulizer you must attest that the patient has failed to use the MDI." I must tell you, it has had a horrible effect, because a lot of elderly patients really could not use the MDI as often as they should. So I think the MDI is perceived as being the very easy answer. Unfortunately, with some of these new technologies, we're broadening the scope of application, and I think that's where we step out of it. I did not look at MDIs in my research for this presentation. I looked at the new technologies that will be discussed at this conference, in terms of what I've been able to read in the literature, and that's disruptive technology.

Rau: I'd like to follow up on comments that nebulizers are sloppy devices for delivering aerosol. We thought that it never mattered when we were delivering β-agonist bronchodilators; maybe that was true and maybe it was not. But that has changed. Now we're beginning to give tobramycin, dornase alfa, pulmicort, morphine, etc, so nebulizer efficiency and ambient contamination are much more of a concern to those of us who work with them. Interestingly, education is the key, and there are data to support this: Christiani and Kern showed that respiratory therapists have an odds ratio of about 2.5 compared to a well-controlled comparison group for developing asthma in the profession.[1] And in a Washington hospital center they documented that the respiratory therapists had detectable blood levels of the R and S isomers of racemic albuterol.[2] That does not establish a cause-and-effect link, but ambient contamination even from apparently benign bronchodilator solutions *may* be linked to occupational asthma. The point is that we are inhaling the medications, and that's one more documentation of it. Carnathan and Martin recently published an abstract regarding respiratory therapists' second-hand exposure to β agonists.[2] And for child-bearing women, ambient contamination from tobramycin is a risk factor for fetal harm. I suspect few therapists have any information about that, and we suspect the patients don't have any knowledge about risk from tobramycin in the ambient air.

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Dunne: Mark Everard attended the Aerosol Consensus Conference we did 2 years ago [published in RESPIRATORY CARE in June 2000], and he wrote an excellent opinion that the ideal aerosol therapy is the clinician having a

clear understanding what the physician wants—picking the right device with the right medication, the right deposition, and the right time.[1] I think that is a formula for success. Unfortunately, I don't see that happening. It's whatever the purchasing agent can negotiate this month for the nebulizer, and who has the lowest generic cost.

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Geller: I want to comment on the compartmentalization of budgets. I've got a couple of examples that show how compartmentalized budgets can conflict with each other and interfere with delivering the best therapy for the patient. One is that on some state levels there's state funding for in-patients and a different organization of the state budgets for out-patients. So if you have, say, a device you want to prescribe to a patient to keep them out of the hospital, that may not be covered by the out-patient guys because it costs a lot of money. For example, the chest physiotherapy *Vest* for a muscular dystrophy patient, which costs several thousand dollars, is not covered by Florida Medicaid, but it might be effective at preventing more costly hospitalization. They don't care because they aren't the in-patient side; they're the out-patient side.

Another example is the hospital budgeting, which goes by department. When an asthmatic comes in, you want to prescribe an inhaled steroid for them as an out-patient, but you want them to get the device in the hospital so you can teach them how to use it correctly. From the hospital's point of view, using MDIs or dry powder inhalers costs them a lot of money for only one day's worth of use. However, the patient learns how to use it correctly and maybe stays out of the hospital the next time. So the global economies sometimes conflict with the microeconomies of the situation. That's frustrating.

Dunne: And I think that's going to have to be challenged if we're going to be able to redesign the health care delivery system. The system as it is right now is not going to be able to sustain itself. As a small employer I can't handle a 25–30%-a-year increase in health insurance premiums. So the employers are being activated. There's going to have to be some change in that myopic, provincial thinking.

Hess: I'd like to back up to something that Joe [Rau] brought up that we haven't talked much about yet at this conference. It has to do with the issue of caregiver protection, which I think is going to become increasingly of concern as newer agents become available. I can tell you that some of our respiratory therapists are very concerned about aerosolizing tobramycin and amphotericin and colistin. We recently did some room sampling, and the aerosol particles are in the room. And the particle sizes are those that get breathed into the lower respiratory tract. Something that I think we might talk about at this conference is what we do about that. We know that it can be an issue with something as simple as albuterol, as Joe brought up. What about some of these other agents?

O'Riordan: We did some work with pentamidine a couple of years ago, and we found that some of the nurses who were administering the treatment had pentamidine urine levels that overlapped those of some of the patients, in terms of the dose, and there was no relationship between the number of patients treated and the level in that particular health care provider. Some people who had very poor technique and very poor supervision of their patients had very high levels, and other people who were very careful had very low levels, though they treated more patients. So we have some expertise in this area from the pentamidine days, and those data are probably applicable to the new agents as well.

Dunne: I would hope that there will be greater awareness in the respiratory therapy community about aerosol therapy. It's not just a ho-hum, mundane undertaking. That's the challenge that I think we're all facing.

Dolovich: I think it's a story not only for therapeutic aerosols, but for diagnostic aerosols as well. When you're doing methacholine challenges all day, you are exposed to the exhaled challenge aerosol. In Canada we place a filter on the exhalation side to protect the respiratory therapist.

Fink:* Harkening back to the days of ribavirin and double-containment tent systems as exceptionally expensive efforts to keep environmental and second-hand exposure to a minimum, it is clear that the small added expense of adding a filter on the exhalation side of a slightly more expensive aerosol system can dramatically reduce second-hand aerosol exposure. It is much more cost-effective to contain the aerosol at the device than to try to protect all the individuals in or out of the vicinity from aerosol exposure.

Rubin: And it's not just exposure of the individual. Anybody who works in an intensive care unit or with chronically ill people knows the specter of drug resistance. One of the best ways to develop drug-resistant microorganisms is to expose microorganisms in the environment to subtherapeutic levels of antibiotics, which is exactly what you do when you release aerosolized tobramycin or other antibiotics into the ambient air at levels far less than what you're delivering to the patient's airways.

Hess: That's the issue. That really is the issue.

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Bringing New Nebulizer Technologies to Market: Regulatory Issues*

Robert J Meyer MD

Regulatory Responsibilities
Regulatory Pathways
Center for Devices and Radiologic Health
Center for Drug Evaluation and Research
Summary

This review outlines regulatory issues involved in bringing new nebulizer technologies to market and describes the regulatory roles of the Center for Devices and Radiologic Health and the Center for Drug Evaluation and Research. The responsible agency is determined by whether a new device involves a new drug formulation. [Respir Care 2002;47(11):1334–1336]

Regulatory Responsibilities

Ordinarily, an application supporting the approval of a new nebulizer would be reviewed by the Center for Devices and Radiologic Health (CDRH) under section 510(k) of the Food, Drug, and Cosmetics Act, under which a nebulizer is a class II device. This means that the application must demonstrate that the new device is substantially similar to a previously available product (called a "predicate" device) in its performance and other key attributes.

However, there has been increasing development of novel nebulization systems that require specific drug formulations, with or without specific containers (eg, a cartridge that is sold only for and fits only in the device being developed). Often these formulations and containers are not otherwise approved and available. When a new nebulizer requires the development of a new drug/device product (ie, the specific formulation and/or its unique container), the regulation of the new drug/device combination would ordinarily occur through the Center for Drug Evaluation and Research (CDER) under the New Drug Application regulations.

This review does not specifically address biologic products administered via nebulization; generally such products and their administration systems would be reviewed through the Center for Biologics Evaluation.

Examples

• A pharmaceutical company develops a hand-held nebulizer to deliver a unique formulation of ipratropium bromide.[1] Because the product does not use available unit-dose nebules of ipratropium, but instead contains a unique formulation, it would be considered a new drug/device combination and would ordinarily be developed and reviewed under CDER and drug regulations. From a regu-

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*Disclaimer: This review represents the opinions and observations of Robert J Meyer MD, based on his expertise and experience, and is not intended to relay official policy of the United States Food and Drug Administration. The contents of this review should not be regarded as binding on the industry or on the Food and Drug Administration.

This report was prepared by Robert J Meyer MD for the 30th Respiratory Care Journal Conference, Liquid Nebulization: Emerging Technologies, held June 28–30, 2002, in Montréal, Québec, Canada. On short notice and unavoidably, Dr Meyer was unable to attend the conference. Thus, although the present report appears in the order it was to be presented at the conference, it is not accompanied by a discussion section.

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latory standpoint this is similar to how new metered-dose inhalers (MDIs) and dry-powder inhalers (DPI) are treated.

- A new nebulizer technology is developed to deliver medication from standard plastic unit-dose vials. Such a new device would be handled by CDRH under the 510(k) regulation, since no new drug product would be developed. This example assumes the new device is intended to administer the drug in a manner consistent with instructions in the drug label and that there is no claim of unique clinical benefit from the drug administered via the new device.
- A new nebulizer is intended to be used with an existing marketed drug, but the new nebulizer uses a different amount of drug than indicated in the marketed drug's label instructions. In this instance the labeling of the marketed drug would need to be changed, and the product would be a combination product (see the United States Code of Federal Regulations, at 21 CFR 3.2(e)(3)).[2] Because the primary mode of action of the combination product is as a drug, CDER would normally be the agency with primary jurisdiction over the combination product.

Regulatory Pathways

Center for Devices and Radiologic Health

Chapter 21 of the Code of Federal Regulations contains all the rules by which the United States Food and Drug Administration (FDA) implements the Food, Drug, and Cosmetics Act, which is the law that, in part, authorizes the FDA to regulate new drugs and devices. These regulations are binding on the industry as well as the FDA. The regulatory definition of a nebulizer (21 CFR 868.5630) reads:

> a) Identification. A nebulizer is a device intended to spray liquids in an aerosol form into gases that are delivered directly to the patient for breathing. Heated, ultrasonic, gas, venturi, and refillable nebulizers are included in this generic type of device.

As such, products meeting that general definition that are able to use existing, marketed drug formulations in a manner consistent with the labeling of the formulations would be reviewed under the device law and regulations. Nebulizers are generally regarded as fitting under section 510(k), under which the sponsor must show that the device is substantially equivalent to a predicate device (ie, a previously marketed nebulizer). The focus of the application and of its review is the in vitro characterization of the nebulizer and its output and the comparison of the in vitro data to those of the predicate device. Device performance elements that must be studied and presented in the application include in vitro testing that focuses on comparative characterization of aerosol emitted from the mouthpiece, including total mass emitted, mass median aerodynamic diameter, geometric standard deviation, and particle size distribution. Biocompatibility testing of the materials may also apply.

Characterization data supporting a new nebulizer are usually acquired via in vitro studies done under nonclinical "Good Laboratory Practice" conditions. The resulting reports should detail the protocols and instruments used, the validation used, and any statistical and clinical considerations for these tests.

Center for Drug Evaluation and Research

If a new nebulizer is considered a new drug/device combination, it would ordinarily be reviewed by CDER, since the primary mode of action is as a drug. Relevant drug laws and regulations are found in section 505 of the Food, Drug, and Cosmetics Act and in 21 CFR 312 and 314. In this case there is no requirement that the nebulizer be equivalent to a predicate nebulizer. As stated above, the development and review for such a product would be very similar to review of a new MDI or DPI. Though it is possible that the entire application would be reviewed by CDER staff, depending on the complexity and novelty of the device proposed, some aspects of the device review may be consulted to CDRH, including electronic circuitry, software, or other novel aspects.

Though it is beyond the scope of this review to detail the expectations for a development program for a new nebulizer (representing a new drug/device combination), the general elements that would need to be addressed in a New Drug Application for such a device include:

- Full characterization of performance in vitro
- In vitro ruggedness testing; life-cycle performance testing
- Pharmacokinetics and pharmacodynamics data with the "to-be-marketed" device (ie, the device used in late-phase studies should be substantially the same in performance and important features as that proposed for marketing)
- Efficacy and safety data with the to-be-marketed device
- Performance in clinical studies, including testing of devices returned for failure and testing of a portion of devices at end of trial for in vitro performance

Summary

New nebulizer technologies may be reviewed by CDRH, CDER, or both, depending on the specifics of the device, its novelty, and whether it requires a new drug formulation or container. Whether developed and reviewed under the device regulations or the new drug regulations, sponsors must adequately characterize the device performance to

assure its characteristics and attributes, and, in some cases, to assure its performance over time.

For those seeking more information, there are a number of helpful Web pages:

For general issues related to CDRH review of nebulizers: http://www.fda.gov/cdrh/ode/784.html

For issues related to incorporation of software into devices: www.fda.gov/cdrh/ode/57.html

For general issues related to MDIs and DPIs, much of which may be useful to a new device/drug combination: http://www.fda.gov/cder/guidance/2180dft.htm

For issues related to new drugs for nebulization: http://www.fda.gov/cder/guidance/4234fnl.htm

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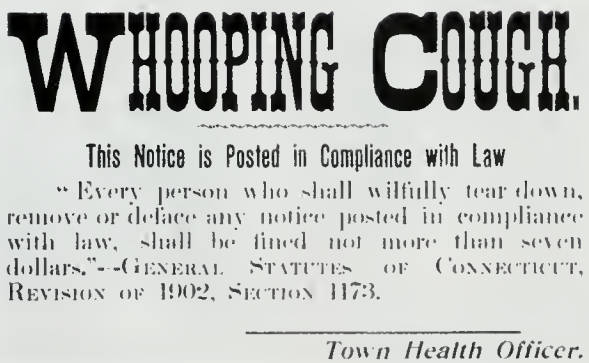

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Books, Films, Tapes, & Software

Drug Delivery to the Lung. Hans Bisgaard MD PhD, Chris O'Callaghan B Med Sci PhD DM, and Gerald C Smaldone MD PhD, editors. (Lung Biology in Health and Disease. Volume 162, Claude Lenfant, Executive Editor.) New York/Basel: Marcel Dekker. 2002. Hard cover, illustrated, 511 pages, $175.

In respiratory care a large proportion of the services we provide, from the home to the intensive care unit, involves administration of medical aerosols. In terms of formal education, respiratory therapists receive several-fold more formal training in aerosol therapy than the vast majority of physicians, nurses, and pharmacists. This has led to the respiratory therapist being seen by the multidisciplinary team as the member with the most aerosol-specific expertise. That said, comprehensive textbooks of respiratory care devote less than 5% of their pages to the topic of aerosols, which is a slim volume of information on which to hang one's hat as an "aerosol expert." To meet our obligations to the team and our patients, respiratory therapists need considerably more information on aerosols than our basic respiratory curricula provide. Unfortunately, textbooks of aerosol science more frequently target the engineer, toxicologist, or environmental scientist than the respiratory or medical clinician. So when 3 physicians with world-class credentials in aerosol medicine joined forces to edit a comprehensive aerosol text, it is only natural to hope that this could be the clinically oriented, authoritative text that we have been waiting for. In this case, the reality has exceeded the expectation.

Drug Delivery to the Lung is the 162nd volume in the Lung Biology in Health and Disease series edited by Claude Lenfant, according to whom this text is "aimed at clinicians, nurses, and respiratory therapists interested in the role of aerosol delivery for optimal management of lung disease" to act as a bridge between basic aerosol science and good clinical practice in the treatment of lung disease.

The content was "inspired by a debate between the authors, with the editors serving as referees." This is borne out in each of the 14 chapters written by clinicians and aerosol scientists, typically from different institutions, who have extensively published seminal research on their respective topics. The result is a dynamic and authoritative text that is both comprehensive and accessible.

The text begins with a history of inhaled drug therapy (Chris O'Callaghan, Ola Nebrink, and Mika Vidgren), which traces the progression of inhalation therapy from smoking the leaves of the *Atropa belladonna* plant (2,000 BC) to Potter's asthma cigarettes (circa 1810) and the first portable nebulizer (1860) to the modern electric compressor/nebulizer of the 1940s and the first pressurized metered-dose inhalers (pMDIs) (1954). The authors provide a chronology of device innovation and applications that have greatly increased over the last 50 years.

The chapter on basic principles of particle behavior in the human respiratory tract (Joachim Heyder and Magnus Svartengren) describes the human respiratory tract as an aerosol filter, the efficiency of which depends on the physicochemical properties of the inspired particles, the breathing pattern, the airway morphology, the mode of breathing (nasal or oral), and the distribution of particles in the inspired air. The developments of the last 2 decades in experimental determination of particle deposition and methods for predicting deposition are reviewed.

"Structure and Function of the Respiratory Tract: Developmental Aspects and Their Relevance to Aerosol Therapy," written by Janet Stocks and Alison Hislop, provides a comprehensive aerosol-centric view of the airways and the developmental changes with age, maturity, and disease in airway structure and function that can affect aerosol therapy.

"In Vitro Testing of Pharmaceutical Aerosols and Predicting Lung Deposition from in Vitro Measurements," by Andy Clark and Lars Borgström, gives a clear and detailed explanation of aerosol characterization techniques, both in vitro and in vivo, with an extensive discussion of issues and limitations specific to nebulizers, pMDIs, and dry-powder inhalers. The literature describing model predictions and in vitro/in vivo correlations specific to nebulizers, pMDIs, and dry-powder inhalers, in vitro versus in vivo variability, and the effect of lung disease are described.

"Factors Affecting the Clinical Outcome of Aerosol Therapy," by Eric Derom and Lars Thorsson, reviews the background, impact on clinical outcome, and clinical relevance of the formulation: patient preference; patient compliance; pharmacodynamic and pharmokinetic properties of the inhaled drug; handling and maintenance of the inhaler; relationship between pulmonary deposition and clinical effect; extrathoracic deposition; adverse effects; systemic effects; and cost effectiveness.

"In Vivo Measurements of Lung Dose," by Mark Everard and Myrna Dolovich, describes pharmacokinetic and imaging techniques (planar γ scintigraphy, single photon emission computerized tomography, and positron emission tomography) in sufficient detail to appreciate the key issues, methods, and relative merits of each technique.

"Targeting the Lungs with Therapeutic Aerosols," by Pieter Zanen and Beth Laube, explores the effect of particle size, inspiratory flow, and inhaled volume on the fate of inhaled drugs. The preferred sites and targets of administration of specific drugs are described, along with the clinical impact of altering the key variables, and considered separately for pMDI, dry powder inhaler, and nebulizer. The chapter concludes with discussion of targeting the lungs during nose breathing, delivery through constricted airways, and delivery to various age groups.

"Nebulization: the Device and Clinical Considerations," by Gerald Smaldone and Peter LeSouef, focuses on the methods of characterizing aerosol output and inhaled mass, and predicting lung deposition, with detailed description of in vitro measurement techniques for adult and pediatric breathing patterns, and in vitro models for mechanical ventilation.

"New Nebulizer Technology," by John Dennis and Ola Nerbrink, provides a tour of new and emerging aerosol technologies, with an excellent overview of the European standard on in vitro assessment of nebulizer performance.

Three chapters are dedicated to the pMDI. "The Metered-Dose Inhaler," by Chris O'Callaghan and Paul Wright, describes the form, function, and performance of pMDIs,

breath-actuated variants, and new inhalers that do not use chlorofluorocarbons. This is followed by a chapter on propellants, by Martyn Partridge and Ashley Woodcock, which tells the story of global warming, the Montreal protocol, and the intricacies of developing the more environment-friendly non-chlorofluorocarbon propellants. "Spacer Devices," by Hans Bisgaard, Jacob Anhoj, and Johannes Wildhaber, thoroughly describes the purpose, design features and use of pMDIs and their spacers and valved holding chambers, as used with adults, neonates, and ventilated patients.

"Dry Powder Inhalers," by Lars Borgström, Hans Bisgaard, Chis O'Callaghan, and Søren Pedersen, discusses the principles of dry powder formulation, how the particles are generated at inhalation, and the implications of resistance for the quality of aerosol generated.

The book concludes with the chapter "Compliance with Asthma Medication," by Michael Hyland and Cynthia Rand, which differentiates unintentional noncompliance (forgetting, instructional problems, device and technique problems, and respiratory insensitivity) from intentional noncompliance (reasoned action/treatment burden, health and illness beliefs, self perception/denial, coping styles, and drug holiday). Methods to diagnose noncompliance are explored, including following clinical outcomes, asking questions and listening, tracking bronchodilator/prophylactic ratio, and using electronic monitors.

The book is attractively bound, showing little signs of wear after rather heavy reading and referencing. There is good consistency of writing styles and illustrations across chapters. The progression of material develops well through the chapters, with many concepts presented first in a broad overview and then explored in greater detail in subsequent chapters. This makes for a good cover-to-cover read.

Unfortunately, it is not quite so easy to spot-reference. The subject index (6 pages) is a bit light and inconsistent compared to the extensive 27-page author index. For example, the index lists mechanical ventilation in the nebulizer chapter, but not in the chapter on spacers, where it was also discussed.

This book will not tell you which device to use or how to use it in your day-to-day practice, but it will arm clinicians with the knowledge necessary to critically evaluate research and clinical outcomes to review and select the best device for each specific situation.

Drug Delivery to the Lung is a must for advanced practitioners, researchers, and educators who need to understand and explain the methods and techniques associated with measurements and administration of medical aerosols. It should be required reading for all graduate-level therapist training programs as well as pulmonary clinical nurse practitioner and pulmonary fellow training programs.

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Airway Remodeling. Peter H Howarth, Jon W Wilson, Jean Bousquet, Sabina Rak, and Romain A Pauwels, editors. (Lung Biology in Health and Disease, Volume 155, Claude Lenfant, Executive Editor.) New York/Basel: Marcel Dekker. 2001. Hard cover, illustrated, 293 pages, $175.

Airway Remodeling is the 155th volume of the Lung Biology in Health and Disease series. This series, edited by Claude Lenfant, Director of the National Heart, Lung, and Blood Institute, is unique in providing scholarly reviews at regular intervals on topics in the pathology, physiology, and treatment of airway and parenchymal lung diseases. Books in this series are edited by authoritative experts in the field, and this volume is no exception.

The term "airway remodeling" has gained increased use over the past 5–10 years. The editors ascribe the first use of the term to Bousquet et al in 1992, although Dr Lenfant points out in his preface that "remodeling" has been used as a descriptive term in lung development and in pulmonary vascular biology since the 1960s and 70s. The introduction of the term "airway remodeling" has led to some confusion. Some authors initially chose to use the term to describe collagen deposition in the airway, but most recently it has been used more expansively, as a summary term for multiple pathologic abnormalities in the airway epithelium and submucosa. So it is useful that the title of the first chapter begins "What Does Airway Remodeling Mean?" in which the authors provide a clear definition.

The book's target audience is specialists in pulmonary and critical care medicine as well as MD and PhD scientists with an interest in airway remodeling. For those groups the book provides a valuable summary of recent data and a useful of overview of the state of the art. Other more clinically oriented groups such as respiratory therapists will probably find the material in this book less useful for their clinical practice, but given the frequent use of the term on rounds, nonphysician health care professionals will find the book a useful reference in which to learn more about what can be a confusing topic. In particular, they will enjoy Björn Jonson's chapter on the physiologic consequences of airway remodeling, and they will also be interested in Peter Howarth's review of the effects of asthma treatment on remodeling.

The organization of this book is similar to others in the *Lung Biology in Health and Disease* series. It is similar in size to a hardback novel, the chapters are relatively short and subdivided by section headings, and most chapters make effective use of tables and figures. The result is a book that is not daunting to pick up and is easy to read and explore. However, the book is expensive ($175), so many potential readers may have to access it via their institutional library rather than buy it for themselves.

Airway Remodeling is divided into 16 chapters that provide concise reviews of important elements of remodeling, including chapters on smooth muscle, collagen deposition, vascular remodeling, and airway innervation. There are also chapters devoted to eosinophils and macrophages, which are thought to be important effector cells in the pathophysiology of remodeling.

Perhaps inevitably in a book that seeks to limit its scope, I found some omissions. The relationship between inflammation and remodeling is alluded to in several chapters but is not tackled directly and perhaps could have been the topic of a separate chapter. In addition, the consequences of remodeling are explored in 2 chapters, but neither really address the mechanisms by which the remodeled airways might contribute to acute airway narrowing during asthma exacerbations (as distinct from chronic airway narrowing). Also, the chapter on animal models, by Johan Kips et al, confined its remarks to discussions of horse, cat, and rodent models of asthma, without any discussion of other useful models such as sheep, monkey, and dog. Finally, there are chapters on eosinophils and macrophages, but it was quite surprising that there was no chapter on the role of the CD4+ T-lymphocyte. Although the role of Th2 (T helper) cytokines is mentioned in several chapters, the data that in-

dicate the central role of CD4 T cells in the pathogenesis of airway remodeling in asthma are compelling and in my opinion warranted a chapter. But these criticisms do not greatly diminish the value of this book. Interest in remodeling is intense and research is advancing knowledge rapidly. This book provides a very good overview of current knowledge and will be a useful and compact source of information about this complex topic.

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Severe Asthma: Pathogenesis and Clinical Management, 2nd edition. Stanley J Szefler and Donald YM Leung, editors. (Lung Biology in Health and Disease, Volume 159, Claude Lenfant, Executive Editor.) New York/Basel: Marcel Dekker, 2001. Hard cover, illustrated, 673 pages, $225.

This text is about asthma—mainly severe asthma—but it covers a lot of core material for anyone interested in asthma pathogenesis and management. Part One covers pathophysiology, with an emphasis on the inflammatory process. Part Two covers pharmacology, and the final part is directed more specifically at management issues. The authors are leading authorities in their respective fields.

The book is directed at clinicians who have a special interest in asthma and its management, largely from a medical model. There is little emphasis on other team members, although the role of the psychologist in assessing childhood asthma is emphasized.

The early chapters are thorough and apply to all aspects of asthma, not just severe disease. Genetics is well covered, although about 18 months out of date, given the explosion of publications in that subject. Airway wall remodeling is covered thoroughly, although the material is descriptive in content as we have little outcome data on that topic. The molecular aspects of steroid action are covered and referred to again later in the chapter on steroid-resistant asthma. Aggravating factors in asthma are reviewed in major chapters on gastroesophageal reflux, upper airway diseases, and aspirin-sensitive asthma. The chapter on infection as a cause of asthma is somewhat out of date, as the *Chlamydia pneumoniae* story has progressed with the publication of management studies that do not seem to support treating this condition as a means of improving asthma status. The chapter on monitoring of asthma is useful and puts sputum cytology and exhaled nitric oxide into context with more traditional tests such as bronchial responsiveness testing, although more detail about hypertonic saline challenge would have been helpful. Steroid adverse effects are thoroughly covered, including growth suppression in childhood and osteoporosis in adults. Chapter 23, "Management of Severe Asthma," might have been more useful if it had integrated a little more thoroughly some of the earlier material—the bottom line is that managing severe asthma is difficult, which will come as no surprise to readers! The editors wrote the final 2 chapters, in which there is a strong emphasis on early diagnosis and adequate treatment early on in the disease to prevent airway remodeling and the development of fixed airway obstruction. The need for national strategies to improve the diagnosis and management of childhood asthma is emphasized.

Like most books in this series, this one is as up to date as possible and contains an excellent bibliography, index, and author index. The use of illustrations is limited, which can make the text heavy-going, and the quality of the computed tomography scans is less than ideal, which weakens chapter 12.

On balance, this is a useful book and will be of interest to clinicians who struggle with patients who suffer severe asthma. Pulmonology residents in training should put this on their list of required reading.

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Asthma: Stop Suffering, Start Living, 3rd edition. M Eric Gershwin MD and EL Klingelhofer PhD. Cambridge, Massachusetts: Perseus Publishing, 2001. Soft cover, illustrated, 262 pages, $17.

Asthma: Stop Suffering, Start Living is a book that is easily read and provides a basic foundation on asthma and allergies. Throughout the text, brief case histories are tied in. Tables, algorithms, and references to other parts of the book enhance understanding of the material. One example in which this is lacking is the reference to FEV (forced expiratory volume). When referred to go to Page 68, there is no text regarding FEV, which should probably be FEV_1.

The authors intended this book for the general public, not for health professionals. Dr Gershwin's specialty as an allergist is evident, as the book does a good job of describing allergies and the role they can play in asthma. The indexed topics give the reader the opportunity to select specific aspects of asthma. The cover of the book describes it as "The complete guide to living with asthma. . . ." Many topics are included but some important issues are not covered. The role the school can play in managing asthma is touched on in regard to the Open Airways program and other programs but could have been expanded to talk about school and family interaction. Since children spend a good portion of their day in school, how the school handles asthma could have a substantial impact on parents and children (preschool included!). The role of spirometry in asthma is also not discussed.

Although I believe the authors' intentions are good, throughout the book asthmatics are referred to as "sufferers" and "victims." As an asthmatic, an asthma educator, and a respiratory therapist, I think that label undermines efforts to help asthmatics feel empowered and to be proactive in their care, which the authors state is one of their goals. The book does a good job of explaining things in words that are easy to understand. The use of patient histories helps create a better understanding of the real world of asthma. The end of each chapter includes a brief summary of topics that were discussed.

Part 1, "Understanding Your Asthma," contains 5 Chapters. Chapter 1 describes what asthma is. The figure on page 13 depicts what a normal airway looks like, but there are no pictures to demonstrate what happens to the airways during an attack. As a picture is worth a thousand words, I think it would be helpful to add that to the next edition. The authors do a good job of differentiating between intrinsic (inherent) and extrinsic (from without) asthma, and the figure on page 20 helps clarify the potentially confusing distinction between those terms. Chapter 2 describes the course of asthma and discusses the notion of "outgrowing" asthma. The explanation of decreasing asthma symptoms as the lungs mature and children get older is simple and to the point. Many people believe that they, or their children, have outgrown their asthma and do not need to monitor their breathing anymore. The story (page 37) of the teenager who became lax in carrying her rescue medica-

tions brings this point home, as she needed to go to the emergency room.

The role of allergies and asthma is thoroughly covered in Chapters 3–5. As this is Dr Gershwin's specialty, the reader will come away with a better understanding of allergies. Other conditions associated with allergies, such as eczema, allergic rhinitis (hay fever), sinusitis, and ear infections, are discussed and provide a better understanding of these conditions and their treatment options. Allergy testing in asthma is discussed and leaves the reader with a good understanding of when it is appropriate and helpful in treating asthma. The role of skin and blood testing (radioallergosorbent testing [RAST] and fluoro-allergosorbent testing [FAST]) and bronchial challenge testing helps to understand ways to identify allergies. Figure 5.1 is a form that can be used to identify possible asthma triggers and, when used effectively, can allow the family and physician to forgo those other tests.

Part 2 is entitled "Avoiding Asthma's Common and Uncommon Causes and Complications." Chapter 6 describes some common triggers: airborne antigens, respiratory infections, exercise, cold air, air pollution, and others. The authors believe that the use of environmental control measures can help reduce some of those triggers. Although a recent review of the role of air purifiers[1] questions their value, some people may benefit from their use in relieving symptoms. Chapter 7 helps answer many questions regarding food allergies. Table 7.4 provides a list of foods that contain certain allergenic food substances such as peanuts. A person with identified food allergies will find that table very helpful. Chapter 8 is on occupational asthma and the possible causes in the work environment. Exercise and sports are common triggers for asthma, dealt with in Chapter 9. The authors suggest swimming as the activity of choice for all asthmatics because of the warm, moist environment. I agree that this activity is one that seems to be less asthma-provoking, but the availability of a pool and climatic conditions often prohibit pool use for many asthmatic children. Physical activity is very important for the development of a child, as the authors point out. The role of medication and warming up before activity is also discussed. Chapter 10 deals with surgery. Chapter 11 addresses pregnancy. Informing the medical team of your asthma history is vital to getting the best outcome in both surgery and pregnancy, and MediAlert bracelets are recommended.

Part 3 is entitled "Caring for Your Asthma." Chapter 12 includes an asthma diary and care plan to fill out with your physician. Compliance is addressed, as well as ways to improve compliance with a plan, which can help some families treat asthma. Figure 12.3 reveals many of the excuses for noncompliance and possible solutions to the problems. Chapter 13 talks about choosing a doctor and provides good information on making sure the physician is concerned about your whole health and is board certified. The role of asthma medications is found in Chapter 14. The use of metered-dose inhalers and nebulizers is discussed. Since it is critical to use inhaler devices properly, the instructions for use on page 189 could be better demonstrated with a series of pictures. The "open mouth" technique is described as: "Aerosol should go straight to the large airways; it should not hit the back of the throat or the tongue." Anyone who has tried the open mouth technique knows that that is easier said than done! More text and pictures should be added to demonstrate how to use the devices and make this book more complete. Even though the authors recommend consulting a pharmacist if you are having trouble with the inhaler, providing that information might prompt them to seek advice.

Medications currently used for asthma are discussed and their use is well explained. The discussion of the MaxAire inhaler describes the larger mouthpiece as a spacing device. I would agree with the authors that using a commercial spacing device is the best way to use a metered-dose inhaler, but I disagree that there are "virtually no differences in brands other than costs." A recent report suggests that the differences among spacing devices can make a difference.[2] The use of nebulizers versus air compressors is also briefly addressed: "Much more effective than metered-dose handheld canisters, the compressor works well for small children, the severely ill, or the elderly." (page 196). Some physicians might debate that notion.[3] Gershwin and Klingelhofer empower the reader to seek other sources of information on drugs (eg, *Physician's Desk Reference* and Web sites) and other health professionals, such as pharmacists and nurses. Unfortunately, there is little mention of the respiratory therapist's role in asthma care. One mention occurs on page 37, a reference to a patient receiving oxygen and a breathing treatment, and another on page 214, a reference to "inhalation therapists, who administer β agonists through special ventilating equipment used in the emergency room." The role of the "inhalation therapist" (the use of that antiquated term is an editorial oversight, I assume) has greatly expanded, especially in the care of asthma patients.

Chapter 15 addresses allergy shots, which builds on the earlier chapter on allergies. Chapter 16 is on care of acute asthma and what you might expect in the emergency room. The last section of this chapter gives some reasons why people can die from asthma. Chapter 17 provides information on summer camps and community programs. Issues such as medications at school and monitoring, which many families face, are not discussed. Chapter 18 is about traveling with asthma and provides a good reminder to prepare for travel with enough medications. The last chapter is devoted to alternative treatments such as homeopathy and acupuncture, and the authors believe those alternatives will not succeed.

Overall, the book provides the intended reader with some good information on asthma and more on allergies, but may leave the reader with some questions concerning proper individualized care. The cost of the book ($17) is reasonable for the information it provides and the additional resources in the appendix. It would be a good book to suggest for families who are new to a diagnosis of asthma and allergies.

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My House Is Killing Me! The Home Guide for Families with Allergies and Asthma. Jeffrey C May. Foreword by Jonathan M Samet MD MS. Baltimore/London: Johns Hopkins University Press. 2001. Soft cover, illustrated, 327 pages. $16.95.

An active home inspector whose specialty is indoor air quality wrote this book as a guide for the prospective homebuyer or homeowner with indoor air complaints. Peppered with fascinating personal anecdotes from his career, it can be used to help determine when to seek professional advice and what to expect from such consultations. The book might also help guide a practitioner who suspects that indoor air quality plays a role in a patient's respiratory disease and building contractors who wish to adopt healthy building techniques. It is not meant to be a reference text nor does it have much to offer the reader interested in the medical/toxicological side of indoor air problems.

The book is well organized, in 4 parts, "Setting the Scene," "Daily Life," which focuses on living areas, "Basements and Attics," and "Clean It Up—Inside and Out." After the introduction that addresses basic concepts of indoor air biology, all the parts are very practical, with useful checklists and recommendations that are clear and easy to follow, such as the description of a simple method to ascertain if a carpet is off-gassing.

The book's emphasis is on the sources and dispersion of bioaerosols that can cause respiratory disease. The opening chapter has a nice description of the biology of fungi and frass (insect excrement), which are 2 important indoor antigens. Many dramatic cases of biological contaminants are graphically and sometimes humorously described, to good effect. For the medical reader there are times when the anecdotes become tedious and one wishes for more specific environmental exposure or medical information. One example is a description of a home in Texas that was ultimately bulldozed because of *Stachybotrys* (a toxic mold) growth that is linked to memory loss and asthma. The lack of association in the medical literature between asthma and *Stachybotrys* isn't mentioned. References are often cursory and without citations, which is frustrating to the medical reader (eg, "a report in an allergy journal theorized that. . . ." and "one study found that over 90% of sinus infections involves fungi.").

The author appears to relish the detective work required in home moisture and mold remediation. His descriptions of what to look for and where are easy to follow. As one might expect, the author has several horror stories involving shower stalls and bathtub leaks with subsequent structural damage as well as health risks. He leaves us with a humorous image of the effects of moisture and subsequent rot on a second floor bathroom, which if not repaired leaves the potential for you to "find yourself sitting on the throne in your living room!" There are good discussions on ventilation, which describe many of the pitfalls of exhaust fan installation and shoddy construction. He does address nonbiological hazards such as chemical irritants, carbon monoxide, asbestos, and radon.

The author appropriately focuses on basements and attics. He provides one of his only aggregate analyses in noting that in his experience people with respiratory problems are almost twice as likely to live in houses with finished, carpeted rooms below grade. One of the extreme difficulties with finished basements is that the moisture damage is often hidden, as compared with unfinished basements. The author describes an interesting technique of placing his sampler in front of an electrical outlet and tapping walls to detect growth behind the sheet rock. The potential hazards associated with furnace blower units are described with illustrative examples.

The author covers attic hazards in a manner similar to that in the discussion of basements. The hazards are those that are entrained through the ventilation system from warm, dark, and moist environments that produce biological hazards, which often enter living areas through the cracks in the attic floor or basement ceiling. These ventilation routes can be detected easily with inexpensive technology such as a blower door, commonly used by indoor air specialists. The author points out that 30–50% of a house's air intake comes from the basement, which is often neglected with regard to clean-up and monitoring of potential hazards. The author describes the "hidden ecology of a damp basement" and provides practical techniques for detecting and stopping sources of external water. He describes the ecology within moist insulation, particularly fiberglass, which supports mold, followed by mold-eating mites and their allergenic hazards, and how allergens can easily be dislodged. He goes on to describe simple methods for preventing such growth. Many of the anecdotal health effects in this section are related to risk of hypersensitivity pneumonitis. In one case he does a nice job of showing how specific allergenic analysis and immunoglobulin E testing can be done. This would have been a particularly useful juncture at which to cite medical literature.

The author recommends vacuuming with high-efficiency particulate absolute (HEPA) filter once a week. He briefly touches on the reservoir action of carpet and how rarely carpets are fully cleaned by vacuuming. In a brush with statistics, he states that in all the hundreds of homes he has inspected he always finds higher air concentrations of particulates in places with wall-to-wall carpets than in those with hardwood, vinyl, or ceramic floor. This is true within homes as well as between homes. He cautions against nonprofessional carpet cleaning, because of the potential for residual moisture and consequent microbiological growth. He describes the persistence of pet allergens in carpeting and uses this hazard to describe a particular irony in the use of professional housecleaning services, in which the vacuum cleaner collects allergens from other homes and in the process of cleaning your home spews them out. He believes that steam cleaning is effective in killing mites, spiders, carpet beetles, and fleas, as well as denaturing allergens in furniture and carpets; that is a potentially important claim, which he attempts to substantiate with 2 experiments, with dust mite allergen and dog allergen. Some of the applications took as long as 30 minutes to achieve effective denaturing, which is perhaps why this technique is not yet supported by the intervention literature.

There is a brief section on air purifiers. With a comic anecdote he points out the fallacy of carbon filters, which rapidly become saturated with volatile organics. He does not endorse HEPA filters in children's bedrooms, which the asthma literature suggests can be effective for asthmatic children. He pounds home the importance of eliminating home allergens first, before purifying the air, because the turbulence created by the air purifier can stir up and increase the airborne allergen load.

The section on schools is very brief, though helpful. The section on office buildings is somewhat more detailed and, again, would benefit from use of some of the now extensive medical literature on indoor air quality problems in office buildings. He does point out flaws in one questionnaire study performed in office buildings where the ven-

tilation rates were doubled and subjects served as their own controls; the flaw was that none of the ventilation rates were low enough to be in the inadequate range. He points out that inadequate ventilation is not the only source of difficulties in most indoor air quality complaints and that bioaerosols are an important source. He cites 2 useful Environmental Protection Agency documents, "Building Air Quality: A Guide for Building Owners and Facility Managers" and "Indoor Air Quality: Tools for Schools," to support this chapter.

In his final chapter, "Closing Remarks: Take Charge," the author describes positive and negative responses to the book. Though he was encouraged by a reader purchasing a HEPA vacuum, he was discouraged if the reader threw out the couch or mattress. He puts the hazards in perspective for susceptible individuals, focusing on those with asthma and allergy symptoms. He encourages people to use their own body's responses to establish the presence or absence of hazards, and cautions not to be deterred if patterns don't emerge. The inability to define or quantify a hazard does not mean the hazard is not present. If air sampling does not support the hypothesis that an indoor air quality problem exists (and it usually doesn't), one cannot necessarily conclude that an indoor air quality problem does not exist. The complicated aspects of ventilation and distribution of allergens often requires professional evaluation. The author points out that the quest for symptom relief is often long and torturous. His final admonition is, "If your house is killing you, trust yourself, take charge, and change the indoor environment."

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Respiratory Care Pharmacology, 6th edition. Joseph L Rau Jr PhD RRT FAARC. St Louis: Mosby, 2002. Soft cover, illustrated, 492 pages, $48.95.

Respiratory Care Pharmacology has become a mainstay in teaching respiratory care pharmacology. Now in its sixth edition, I am confident that most if not all respiratory therapists have encountered this textbook. This newest edition continues with many strengths of the previous editions and provides new material. With 13 distinguished contributors and 4 reviewers, this text offers current information in a comprehensive, readable book for respiratory therapists and other health science readers.

This newest edition offers an updated and organized approach to pharmacology. It is divided into 3 units: (1) Basic Concepts and Principles in Pharmacology, (2) Drugs Used to Treat the Respiratory System, and (3) Critical Care and Cardiovascular Drug Classes. Along with a detailed table of contents, there are a number of pedagogical features that facilitate better conceptualization of the material, including an individual chapter outline, an initial paragraph summarizing each chapter, and boxed summaries of key concepts. At the end of each chapter are self-assessment questions, clinical scenarios, a summary of key terms and concepts, and an up-to-date reference list. I found the author's use of examples to be effective in illustrating many of the concepts. Most of the chapters contain many examples. On page 18 the phrase "for example" is used 5 times, and this is common throughout the book. In addition, I was particularly interested to find, in most chapters, brief historical perspectives on many of the drugs discussed.

Several chapters include a summary of how to assess the use of particular drug groupings—a feature particularly useful for students. For example, in Chapter 6, "Adrenergic (Sympathomimetic) Bronchodilators," the section on "Respiratory Care Assessment of β-Agonist Therapy" details what needs to be assessed and monitored when providing β agonists. This section also emphasizes which key points to instruct the patient on, which cardiopulmonary variables to monitor, and differentiates assessment for quick-acting and long-acting β agonists.

The authors include appropriate references to National Institutes of Health guidelines for asthma and the Global Initiative for Chronic Obstructive Lung Disease; the details of both sets of recommendations are included in the appendixes.

The above features help make this an excellent text for both students and advanced practitioners, as a reference or as a review of current standards in respiratory care pharmacology.

Chapters 1 and 2 provide an in depth coverage of principles of drug action with a fully illustrated introduction to pharmacology, the drug administration phase, and pharmacokinetics, but these chapters do not explain certain concepts that an entry-level student may need to understand. For example, on page 29, the discussion on G protein-linked receptor activation and G protein function would be daunting for some student readers.

Chapter 3 discusses administration of aerosolized medications. I found this chapter comprehensive, covering all aspects of aerosol delivery. Physical principles and aerosol delivery devices are discussed, with state-of-the-art information provided. However, I would like to have seen more in the section on patient-device interface issues, such as the limitations of mask therapy and variables that influence aerosol delivery during mechanical ventilation.

Chapter 5 discusses the central and peripheral nervous system. As a seasoned reader, I found this chapter easy to understand, but students find this topic challenging. Nevertheless, having read about this topic in several other textbooks I am not sure that any other approach would be more effective than how the material is presented in this book.

Unit II covers drugs used to treat disorders of the respiratory system. These include adrenergic and anticholinergic drugs, xanthines, mucus-controlling drugs, surfactant agents, corticosteroid and nonsteroidal agents, antimicrobial and anti-infective agents, and drugs to control cough. Each of these topics is covered in depth, with indications for each drug group, discussion of specific drugs, modes of actions, routes of administration, and adverse effects. Comprehensive tables of dosages of various preparations are provided throughout this section. For example, Table 6.1 on page 110 includes generic and trade names of all available adrenergic bronchodilators, along with which receptors are stimulated, adult dosages, and time courses.

I was impressed with Chapter 9, "Mucus-Controlling Drug Therapy," because of its detail on physiology of mucus flow, nature of mucus secretions, and physical properties of mucus. This chapter includes a discussion of common drugs used to promote mucus expectoration such as N-acetyl-L-cysteine, dornase alfa, and expectorants. Other drugs are also discussed, such as F-actin depolymerizing drugs, mucokinetics, antiproteases, gene-therapy related drugs, and mucoactive agents. Since the primary focus of most respiratory care procedures and treatments is to improve mucus rheology and promote expectoration, it is para-

mount for practitioners to understand the ideas found in this chapter.

Unit II also includes 2 useful chapters on selected agents for various respiratory-related conditions such as α-antitrypsin deficiency, smoking cessation, and clinical use of nitric oxide. There is also a chapter on neonatal and pediatric medicated aerosol therapy. I found the section on nicotine replacement therapy a good overall summary of how these drugs work, but I would like to see this section expanded to cover the topic in more detail, since many respiratory care textbooks lack this discussion and there are now smoking cessation programs in many hospitals. The neonatal and pediatric chapter offers up-to-date dosing schedules for many respiratory-related drugs. Important factors influencing medicated aerosol therapy are also included. I think Table 17.2, which compares neonatal and adult respiratory variables (eg, tracheal diameter, dead space volume, inspiratory flow), will be particularly useful to students in understanding the factors that influence aerosol delivery in neonates and adults.

Unit III includes coverage of cardiac and vasoactive drugs, including drugs that affect circulation (eg, hypertension therapy, diuretics) and drugs that affect the central nervous system. Chapter 19 introduces cardiac drugs and provides only brief information on many common drugs such as dopamine and dobutamine. I would like to have seen more about clinical application of the inotropic drugs. In addition I found only a brief mention of norepinephrine and nowhere in the book was Levophed mentioned, though it is commonly used for acute hypotension. Chapter 20 discusses drugs that affect circulation and includes a sketchy overview of the etiology and pathophysiology of hypertension. Hypertension therapy, nitrates, and vasopressors are also discussed. The section covers inotropic drugs briefly, although this is redundant since they are also covered in Chapter 18. This chapter provides a good section on antithrombotics and anticoagulants.

The book concludes with 4 appendixes, which include answers to the self-assessment questions, units and systems of measurements, recommendations for using aerosol generators, medical management of asthma and obstructive diseases, and a glossary.

My suggestions to improve this book relate mostly to the illustrations. The entire book uses 2 colors: black print and shades of green for illustrations. I find black with gray scales in line drawings and graphs better to illustrate concepts and detail. The only illustration with a hint of dimension is of the kidney (Figure 21.1), in which a degree of shading helps bring the illustration to life. I am not sure why other illustrations lack that type of presentation.

The shades of green in the graphs and histograms make it difficult to discern differences in the data presented. For example, Figure 3.20 uses shades of green to illustrate patterns of aerosol loss, but the colors used are not distinct enough to differentiate the data, and the point of the illustration is difficult to determine. Green line drawings are used in Chapter 3 to illustrate aerosol generators (eg, metered-dose inhalers and dry powder inhalers) and metered-dose inhaler reservoirs. I believe that photographs would better serve the reader in visualizing devices. Chapter 11 discusses various inhaled steroids, and photographs of the delivery devices are needed to support the discussion.

On page 237 there are 3 black-and-white electron micrographs of the degranulating mast cell. Perhaps the addition of a normal mast cell micrograph for comparison would benefit the reader. Also, in the black-and-white photograph in Figure 9.10, which is supposed to illustrate the effects of dornase α, it is difficult to see exactly what the author is trying to show.

The call-out for Figure 11.1, which illustrates the kidney, is on page 208, but the figure is on Page 210. Again, the simple use of spot color is ineffective in illustrating the structure of the kidney and adrenal gland.

I would like to see the end-of-the-chapter section, titled "Respiratory Care Assessment," that is found in some of the chapters, included in each chapter that deals with drugs, such as Chapters 18 and 22.

Despite these limited criticisms and suggestions, I found **Respiratory Care Pharmacology** to be well written and believe it serves the profession well. It will continue to be a staple in respiratory care education.

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Airway Cam Video Series, Volume 3: Adult Intubation. Richard M Levitan MD and E Andrew Ochroch MD. Wayne, Pennsylvania: Airway Cam Technologies. 2000. VHS video cassette, 28 minutes, $149.95.

After I completed 4 years of internal medicine training, I remember thinking with some satisfaction that I had become quite accomplished in intubating the airways of unstable patients with acute respiratory failure. And I also remember realizing after doing my first few bronchoscopies as a pulmonary fellow that I had previously no clear visual understanding of upper airway anatomy from the perspective of a physician with a laryngoscope and endotracheal tube in hand, anxiously peering down a hypoxic patient's throat. Despite prior efforts to learn airway anatomy from drawings and photographs of the upper airway, there was nothing like actually being there. Cruising through the upper airway with a bronchoscope leisurely checking out airway landmarks and the distance of one structure to the next did more to enhance my intubation skills than all of my previous efforts combined.

With those reflections in mind, I was pleased to review volume 3 of the Airway Cam video series, **Adult Intubation** by Richard Levitan MD and Andrew Ochroch MD. This 28-minute video provides an in-depth view of airway anatomy from the entrance of the nose and mouth to the larynx, as seen from 3 perspectives: through a fiberoptic rhinolaryngoscope; through a rigid, mirrored laryngoscope; and via the Airway Cam video camera, which simulates the clinician's view while performing laryngoscopic transoral endotracheal intubation. The video also presents a specific discussion of the various laryngoscope blade designs and the related intubation techniques.

The video begins with a review of hypopharyngeal and laryngeal landmarks as identified by a drawing of the upper airway. These landmarks are later called out as they are viewed during laryngoscopy. The video proceeds to a physician subject who conducts fiberoptic rhinolaryngoscopy on himself and phonates as anatomic structures come into view. The trip through the upper airway is well worth the price of admission if one can ignore the operator's eerie infatuation with his own vocal cords as he phonates "eeee" over and over again for several minutes. The orientation gained by the trip would definitely promote intubation skills, even though the projection of the airway is

inverted, as compared with the view seen during transoral intubation.

The next ride through the airway is taken with a rigid mirrored laryngoscope, which provides a more close-up view of glottic structures. The stroboscopic images of the vocal cords oscillating in slow motion during phonation are interesting but seem somewhat out of place in a video on airway intubation. But that (and scenes of a physician viewing his own airways with a fiberoptic laryngoscope) is apparently the price you pay for an otherwise excellent video done by otolaryngologists.

But viewers arrive at their destination as they come upon the review of laryngoscopic blades and the Airway Cam images of the upper airway during actual intubations of patients in controlled settings. The intubations are entirely the real thing, with a demonstration of realistic difficulties with the use of various blades and in a wide spectrum of patients. The images are sharp, vivid, and clearly representative. The commercial narrator seems familiar with the topic and avoids the usual mispronounced medical words or canned formalities of the typical video series.

The laryngoscopic views of the airway during intubation build on the lessons learned earlier in the tape that prepare the viewer for what anatomic sites to expect as they glide down the airway. Although I have no personal experience with several of the laryngoscopic blades reviewed, the video supports my preference for the curved Macintosh blade for most patients.

The video is not geared specifically for respiratory practitioners who perform urgent intubations for acute events. There are no comments regarding face mask bag ventilation, signs of esophageal intubation, or protocols to ensure adequate oxygenation during intubation attempts. But such was not the intent of the series. The lessons presented in the video clearly extrapolate to the emergency setting. I was especially pleased to hear comments about the importance of an assistant compressing the cricoid cartilage to prevent esophageal regurgitation and aspiration, and the value of the operator manipulating the laryngeal cartilage to bring the glottis into view. Also, the video spent a warranted amount of time emphasizing the proper head and neck positioning for intubation and special positioning issues with obese patients.

If I were responsible for honing the intubation skills of clinicians learning emergency intubation, I would definitely include this video in the airway curriculum. The video is also relevant for respiratory therapists and technicians, nurses, and physician respiratory therapy directors who do not intubate but assist with intubation or supervise the emergency response team. There is nothing like a personal fiberoptic trip through the airways to learn airway anatomy. This videotape is the next best thing.

John E Heffner MD
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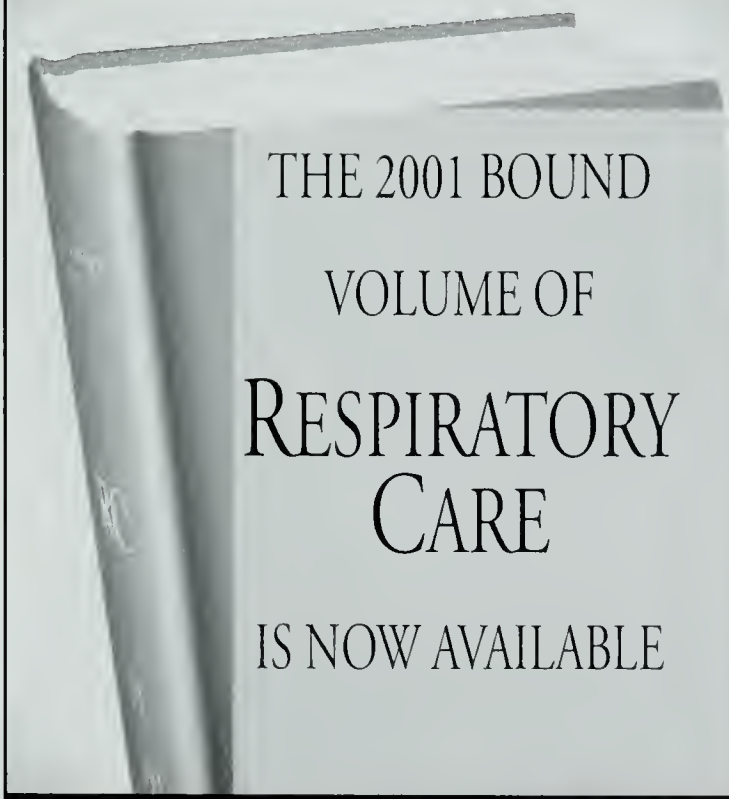

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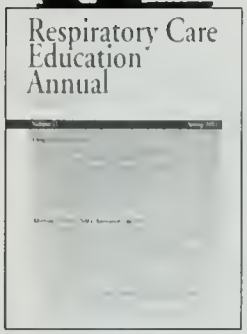

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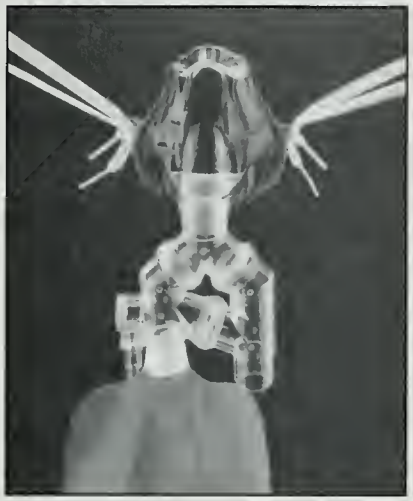

Disposable Mask. VIASYS Healthcare introduces the Hi-Ox^{80}, which they describe as a new technology oxygen delivery system and the only disposable mask capable of delivering >80% oxygen at only 8 L/min. This technology was designed to meet the needs of post-op patients for infection and nausea reduction, according to the manufacturer. VIASYS states that delivering high F_{IO_2} at one-half to one-third the flow of other devices has implications for hospitals and field applications where oxygen resources are limited by tanks or flow. For more information from VIASYS Healthcare, circle number 192 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Peak Flow Monitor. Ulster Scientific Inc. has introduced its new Kidz-Med Whistle Watch®, an affordable peak flow monitor that enables parents to effectively monitor their children's asthma, according to the manufacturer. Ulster Scientific Inc claims that regular use of the Kidz-Med Whistle Watch is especially helpful in monitoring the use of prescription asthma medication for younger children and results in better asthma management and reduced medication use and hospital costs. The company says this device is easy to use: after taking a deep breath, the patient blows as hard as possible into the mouthpiece of the monitor. If a whistle sound is heard, the asthma is under control. If the patient cannot produce a whistle, asthma treatment recommended by the doctor or other health care professional should be followed. For more information from Ulster Scientific, circle number 193 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Medical Pocket Light. The Sabre Free-Hand High Intensity Medical Pocket light, being introduced by Sabre Medical Instruments LLC, features a bright 6,000 candlepower lamp with a clear lens and a universal adapter that can hold a standard tongue blade and/or a culture swab to permit one-handed examinations. According to the manufacturer, the product is made of high-impact plastic and the light is waterproof and can be cleaned using cold sterilization techniques. It runs on 2 AAA batteries. Optional accessories include disposable stainless steel and nylon illuminated cerumen removal loops that eliminate the need for additional light sources and allow one-handed ear treatments. For more information from Sabre Medical Instruments, circle number 194 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Therapeutic Breathing Device. InterCure Inc has announced FDA clearance to sell their therapeutic device, RESPeRATE, over the counter. This battery-operated device is designed to help patients with breathing exercises designed to lower blood pressure. According to the manufacturer, the device analyzes patients' breathing patterns and instantly composes personalized musical tones to guide breathing exercises. Users place an elastic belt with a respiration sensor around their torso, above their clothing, and wear standard headphones. RESPeRATE automatically analyzes the user's breathing rate and pattern and then interactively guides the user through a therapeutic breathing exercise that slows the breathing from a normal rate of 14-18 breaths per minute to the "therapeutic zone" of less than 10 breaths per minute with prolonged exhalation, according to InterCure. For more information from InterCure Inc, circle number 195 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

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Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

Scheduled Professor's Rounds 2003

#1 Weaning the Long-Term Ventilator Dependent Patient — David J Scheinhorn MD/David J Pierson MD FAARC
Live March 11; Audio April 15

#2 Management of Pediatric ARDS — Michael Anderson MD/Timothy R Myers RRT
Live April 8; Audio May 13

#3 Implementing Protocols: What Have We Learned About Being Successful? —Richard M Ford RRT FAARC/Sam Giordano MBA RRT FAARC
Live May 6; Audio June 10

#4 Improving Patient Safety in Acute Care Hospitals: What Do Respiratory Therapists Need to Know? — Karen J Stewart MS RRT/Kevin Shrake MA RRT FAARC
Live June 3; Audio July 8

#5 Legal Issues that Impact the Practice of Respiratory Therapists —Anthony Dewitt JD RRT FAARC/ Sam Giordano MBA RRT FAARC
Live August 12; Video September 16

#6 Asthma Disease Management: What's New and How Is It Working? — Thomas J Kallstrom RRT FAARC/Timothy R Myers RRT
Live September 9; Video October 14

#7 Sedation and Paralysis in the Mechanically Ventilated Patient — William E Hurford MD/Dean R Hess PhD RRT FAARC
Live October 7; Video November 7

#8 Blood Gases: Doing It Right from Collection Through Analysis — Carl D Mottram RRT RPFT/ Richard D Branson RRT FAARC
Live November 4; Video December 2

Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
- — Current job listings
- — American Respiratory Care Foundation fellowships, grants, & awards
- — Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
- — Subject and Author Indexes
- — Contact the editorial staff
- — OPEN FORUM; submit your abstract online

Asthma Educator - Certified (AE-C)
http://www.naecb.org

Asthma Management Model System
http://www.nhlbi.nih.gov

Keys to Professional Excellence
http://www.aarc.org/keys/

Committee on Accreditation for Respiratory Care
http://www.coarc.com

The National Board for Respiratory Care— Examination Fees for 2002/2003

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RPFT	$250 (new applicant) $220 (reapplicant)
RRT (Written & CSE)	$190 (new) $150 (reapplicant) written only $200 (new and reapplicant) CSE only $390 (new) $350 (reapplicant) both

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, or e-mail: nbrc-info@nbrc.org

American Association for Respiratory Care

MEMBERSHIP APPLICATION

ACTIVE MEMBER
An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC.

ASSOCIATE OR SPECIAL MEMBER
Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field

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Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

Please read the eligibility requirements for each of the classifications above, then complete the form. All information requested must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

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  - ☐ Physician
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- ☐ Medical Director
- ☐ Student
- ☐ Staff Nurse
- ☐ Other, specify _____

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- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Hospital/Acute Care
- ☐ Manufacturer or supplier
- ☐ Outpatient Clinic
- ☐ Physician office
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- ☐ Other, specify _____

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- ☐ Associate Degree
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- ☐ Master's Degree
- ☐ Doctorate Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

Job Status

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- ☐ Part Time

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- ☐ CRT
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- ☐ CRNA
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- ☐ LVN/LPN
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Payment must accompany your application to the AARC. Fees are for 12 months. These fees contain the $12.50 new members processing fee. Renewing members (except students) can deduct $12.50.

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I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is cause for rejection or expulsion.

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Hess D. New therapies for asthma. Respir Care (year, in press).

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Article in a publication that numbers each issue beginning with Page 1:

Kallstrom TJ. Focus on asthma—disease management: a role for the respiratory therapist. AARC Times 1999;23(Oct):16, 17, 19.

Corporate author journal article:

American Association for Respiratory Care. Clinical Practice Guideline. Removal of the endotracheal tube. Respir Care 1999;44(1):85-90.

Article in journal supplement: (Journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval.)

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Volsko TA, De Fiore J, Chatburn RL. Acapella vs flutter: performance comparison (abstract). Respir Care 2000;45(8):991.

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Giordano SP. What's that sound? (editorial) Respir Care 2000;45(10):1167-1168.

Editorial with no author given:

The perils of paediatric research (editorial). Lancet 1999;353(9154):685.

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Cairo JM, Pilbeam SP. Mosby's respiratory care equipment, 6th ed. St Louis: Mosby; 1999:76-85.

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American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

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World Wide Web

American Lung Association. Trends in pneumonia, influenza, and acute respiratory conditions mortality and morbidity. February, 2000. http://www.lungusa.org/data. Accessed November 20, 2000.

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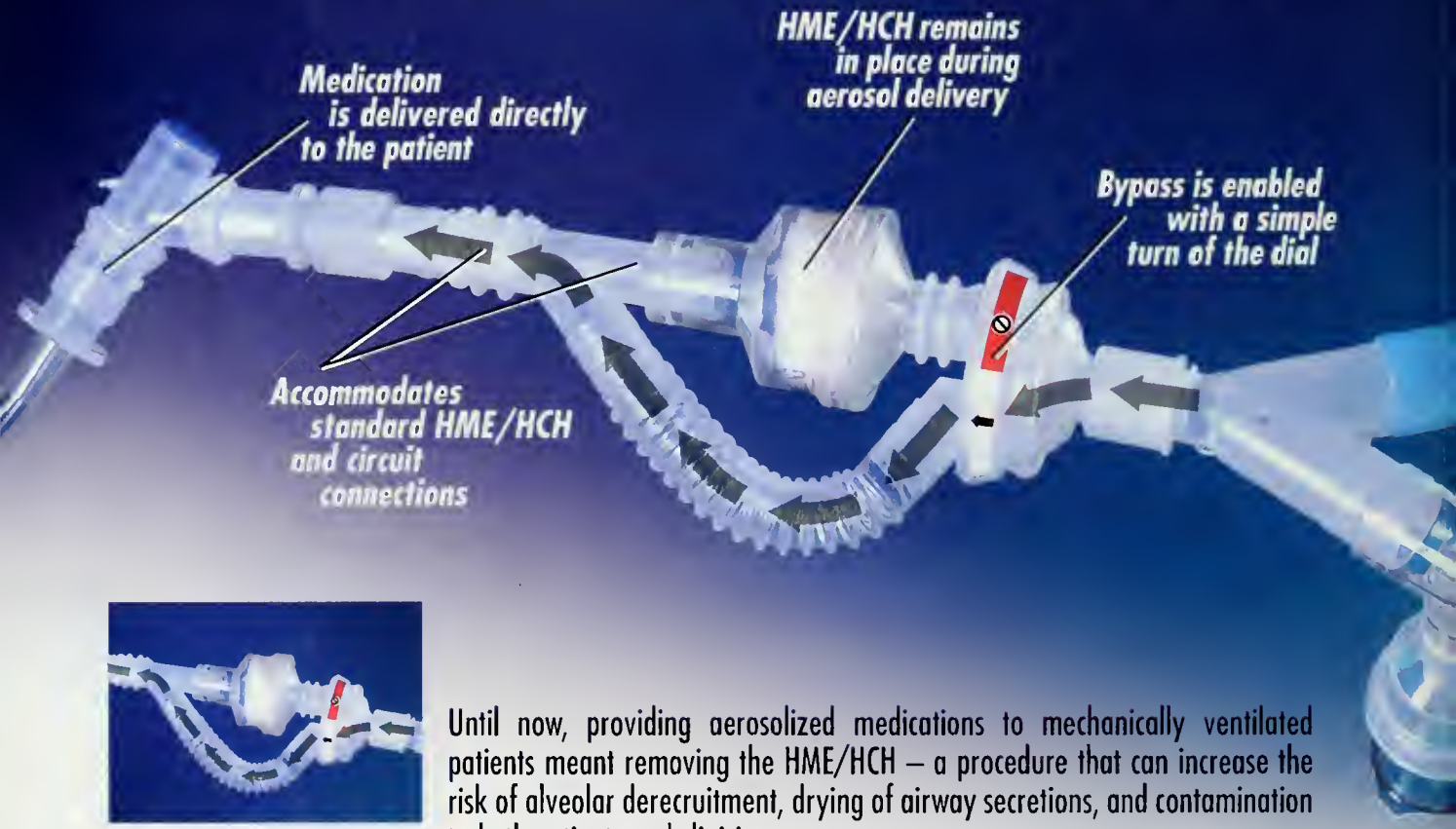
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